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Effect of Pregnancy on the Course of Heart Disease

Re-evaluation of 106 Cardiac Patients Three to Five Years after Pregnancy

By MARY M. MILLER, M.D. AND JAMES METCALFE, M.D.

One hundred and six patients have been restudied three and one-half to 5 years (average 4.1 years) after they were observed with pregnancy and heart disease at the Boston Lying-in Hospital.

This re-evaluation indicated that the altered circulatory dynamics of pregnancy may temporarily decrease functional capacity. However, no permanent change in degree of heart disease could be directly attributed to the pregnancy for which these patients were followed in 1950 and 1951.

THE woman with heart disease who has entered or is planning pregnancy will ask a series of questions involving her immediate and remote prognosis. One of the questions involves her chance of surviving pregnancy. Many studies have been reported evaluating the mortality during pregnancy and the puerperium in women with heart disease. This mortality varies from less than 1 per cent to more than 3 per cent in patients under careful medical management throughout their pregnancies. As pointed out by Hamilton[1] in his recent summary of cardiovascular problems in pregnancy, the immediate maternal mortality will be influenced by the severity of the heart disease at the time of pregnancy judged by a careful review of the patient's history, with particular regard to the previous occurrence of episodes of heart failure, the maternal age, the availability of good medical and obstetrical advice and the cooperation of the patient in accepting this advice. It will also be affected by the policy of the patient's physicians toward the interruption of pregnancy, since if pregnancy is interrupted early in all patients with severe heart disease, the immediate maternal mortality might decline, possibly at the cost of an increased fetal mortality.

A second question to be expected from the woman with heart disease entering pregnancy is what chance she has of producing a living infant. The infant mortality when the mother has heart disease has been studied in several large clinics. Bunim and Appel[2] reported an infant mortality rate of 6 per cent in women with compensated heart disease and one of 15 per cent for infants of mothers in congestive heart failure, excluding the fetuses lost through therapeutic interruption. If to this is added the fetal mortality due to therapeutic interruption of pregnancy, the total fetal mortality may be as high as 35 per cent in women with congestive failure during pregnancy. Litzenberg[3] in a recent review of

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This work was done by Dr. Metcalfe during the tenure of an Established Investigatorship of the American Heart Association.

the literature states that the mortality of infants born to patients classified functionally in class I and II by the American Heart Association Classification will be the same as in patients with no heart disease, while those born of mothers in class III and IV, under the same classification, will have a 30 per cent mortality.

Thus, these two questions can be answered in fairly definite terms. The woman with well compensated heart disease, who is class I or class II by the functional classification of the American Heart Association, has better than a 97 per cent chance of surviving pregnancy and about as good a chance of producing a living baby as the woman without heart disease.

A third question that the pregnant woman with heart disease logically may be expected to ask is in regard to her prognosis for life and health, once the immediate dangers of pregnancy are past. Few data are available to answer that question. For this reason a follow-up study of those women with heart disease who were seen during pregnancy in the Boston Lying-in Hospital is being made. This is the first report on that study.

Material

In July 1950 Dr. C. Sidney Burwell and his associates assumed responsibility for the medical clinic at the Boston Lying-in Hospital. In the ensuing 18 months, 91 cardiac patients were delivered, and an additional 15 patients, delivered shortly before July 1950, were seen and evaluated at a postpartum visit to the medical clinic. This total of 106 patients included 92 with rheumatic heart disease, 8 with congenital heart disease, 1 with hypertensive cardiovascular disease, 1 with combined hypertensive and rheumatic heart disease, and 4 with "potential" rheumatic heart disease. The patients, at the time of pregnancy,* were classified according to functional capacity (American Heart Association Classification) as follows:

No heart disease†	4
Class I cardiac disease	64
Class II cardiac disease	19
Class III cardiac disease	14
Class IV cardiac disease	5

In the group there were 16 interruptions of pregnancy because of heart disease, 2 interruptions for noncardiac reasons, and 4 spontaneous abortions. Eighty-four patients continued through pregnancy (81 of these had a living baby).

There were no maternal deaths during pregnancy or in the postpartum period in this group of 106 patients.

These 106 patients were recalled in order to study the evolution of the mothers' heart disease, and thereby to clarify the course of cardiac patients following pregnancy. The re-evaluation was accomplished in a 6-month period between January and June, 1955. The planned work-up included history, physical examination, vital capacity, electrocardiogram, fluoroscopy with barium swallow, and routine chest film. Such a study was completed in 85 patients who came to the clinic, while a history was procured by telephone or letter in the remaining 21 patients who could not report for more specific study.

This group of 106 was selected only in so far as it comprised *all* the patients followed within a specified time interval in a metropolitan obstetrical hospital and referred to the hospital's medical clinic because of heart disease. The follow-up period of 3 to 5 years was selected because the changes since pregnancy could be evaluated by the same group of physicians that had supervised the therapeutic regimen during pregnancy. While the follow-up period is short, re-evaluation after even this time serves to indicate certain trends in cardiac patient behavior. Reports of all examinations made were sent to family doctors or to local clinics. The patients were

* Patients were classified as to functional status at the eighth month of pregnancy or at the time of interruption. Ideally their pre-pregnant classification should have been used but we did not see them until they were pregnant.

† Patients with symptoms or signs referable to the heart but in whom a diagnosis of cardiac disease is uncertain. At the time of pregnancy heart disease could not be excluded in these patients.

again classified as to functional capacity (American Heart Association Classification) as follows:

No heart disease	8
Class I cardiac disease	67
Class II cardiac disease	21
Class III cardiac disease	7
Class IV cardiac disease	0
Dead	3

The changes in classification between the original examination (July 1950–December 1951) and the present examination (January 1955–June 1955) are shown in table 1.

As shown in table 1, the 4 patients who were classified during pregnancy as "no heart disease, undiagnosed manifestation" were, on re-examination, found to have no heart disease, but only a predisposing etiologic factor, rheumatic fever. The total group now classified as having no heart disease also includes 4 patients originally placed in class I. The other 60 patients who had been in class I are classified at the present time as follows: 50 in class I, 8 in class II, 2 in class III. Of the 19 patients originally in class II, there are at present 9 in class I, 8 in class II, 1 in class III and 1 dead. The 14 patients who were in class III are now classified as follows: 5 in class I (improvement in 1 after valvuloplasty), 5 in class II (improvement in 1 after valvuloplasty), 3 in class III, and 1 dead. Of the 5 patients who were class IV during pregnancy, 3 had a valvuloplasty performed after delivery and are now in class I; 2 did not have valvuloplasty, and of these, 1 is now in class III and 1 is dead.

Thus re-evaluation revealed an unchanged functional classification in 65 patients and an *improvement* in classification in 27 (5 with valvuloplasty). There was worsening of heart disease in terms of functional classification in 14 patients. These data are summarized below:

Total patients		106
After 4.1 years		
Dead	3	
Worse	11	
Unchanged	65	
Better	27	

TABLE 1.—*Comparison of Functional Classification during Pregnancy with Functional Capacity at Re-evaluation Three to Five Years after Pregnancy in 106 Women with Heart Disease*

Original Class	Present Class					
	No heart disease 8	I—67	II—21	III—7	IV—0	Dead 3
No heart disease 4	4					
I—64	4	50	8	2		
II—19		9	8	1		1
III—14		5	5	3		1
IV—5		3		1	0	1

The number of patients in each functional class *during* pregnancy is indicated at the left hand column of the table. The number of women in each class at re-evaluation is indicated at the top of the table. The origin of each of the present groups can be determined by locating them horizontally in the table so that their original classification is seen at the left. The heavily outlined squares contain the numbers of patients whose classification has remained the same. To the left of these squares are seen the number in each of the original classes whose present classification is improved. To the right of the darkly lined squares are seen those whose present status is functionally worse than when evaluated during pregnancy.

In 6 of the 27 patients who showed an improvement in functional classification, the change was attributed to an operative procedure performed since pregnancy. One patient with a coarctation of the aorta was much improved following excision of this lesion.* Five valvuloplasties were performed after pregnancy for relief of mitral stenosis, with definite improvement in each case. In some of the other patients in whom functional classification improved, the improvement may have been more apparent than real; the altered dynamics of pregnancy may well have temporarily diminished functional capacity. In other instances there may have been spontaneous

* A second patient with a coarctation of the aorta was not operated upon because of an associated papillary cystadenocarcinoma of the ovaries; a third patient has done so well that excision has not been advised.

healing of inflammatory valvular lesions in the interval between the 2 examinations.[4]

In the group of 14 patients who showed worsening of heart disease, there were three deaths. These are discussed later. The remaining 11 patients may be compared with those who showed improvement or no change in functional classification. The group that showed progression had an average age of 31.5 years, which did not differ significantly from the average age of 33.1 for the improved group, or 31.7 for the unchanged group. The average number of pregnancies in the patients who progressed was 2.6 per patient, which does not differ from the average of 2.5 for the improved group,† or 3.1 for the unchanged group. The patients who are now pregnant include 3 of the 11 who progressed, 2 of the 27 who improved and 4 of the 65 who remained unchanged.

Of the 11 patients who showed progression, the three who are now pregnant note increased symptoms during their present pregnancies. The progression of heart disease in the other eight patients of this group does not appear to be directly related to past pregnancies. It seems rather to be a result of the evolution of rheumatic heart disease.

The three deaths in the total group of 106 patients were all confirmed by official copies of Certificates of Death. These three patients are of such interest and significance that their histories will be outlined.

The first patient had a diagnosis of both hypertensive cardiovascular disease and rheumatic heart disease with mitral stenosis. She was first seen at the age of 27 with a past history of recurrent rheumatic fever and of hypertension of nine years' duration. There had been a miscarriage at 20 weeks' gestation at the age of 26. The only symptom during the pregnancy for which she was seen was persistent headache. Physical examination revealed elevated blood pressure (190/110–210/120), grade II eyeground changes, and an enlarged heart with signs of mitral stenosis and mitral insufficiency. There was electrocardiographic and x-ray evidence of left ventricular hypertrophy. Her functional classification was class II. The pregnancy was interrupted at five months gestation, and the patient was sterilized. She died three years later of a cerebral vascular accident.

The second patient was seen first at the age of 25 with a clear history of multiple attacks of rheumatic fever and with physical findings of mitral stenosis, mitral insufficiency, aortic stenosis and aortic insufficiency, as well as atrial fibrillation. She had a history of a normal full-term delivery at 21, and a spontaneous abortion at three months at the age of 22. This patient had congestive heart failure early in the pregnancy for which she was seen at the Boston Lying-in Hospital. Her functional classification was class III. Electrocardiographic and x-ray abnormalities were present. The pregnancy was interrupted in the third month and the patient was sterilized. She died four years later, and autopsy showed evidence of acute rheumatic fever, as well as multiple valve lesions.

The third patient, 40 years old when first seen, had rheumatic heart disease with both aortic and mitral valvular disease. There was a past history of a single attack of rheumatic fever. She had taken digitalis irregularly for a period of 13 years. She had delivered a stillborn child at 23; two subsequent pregnancies were complicated by toxemia, but viable babies were delivered by cesarean section. History and physical examination during the fourth pregnancy revealed early cardiac failure. Her functional classification was class IV. Electrocardiogram showed left bundle branch block; chest x-ray films revealed cardiac enlargement and increased vascular markings. The patient was admitted for interruption, but had a spontaneous abortion at three and one half months. Her failure cleared and she returned to work. She died six months later in another attack of cardiac failure.

Therefore, three patients, in a total of 106, died during the 3 to 5 year follow-up period. They were all severely ill cardiac patients and evidence indicates that the pregnancies for which they were seen did not contribute

† This calculated average excludes one patient who had 16 viable babies; inclusion of this unusual patient would give an average for the improved group of three pregnancies.

directly to their deaths. Indeed, none of these three patients underwent the full circulatory burden of pregnancy. It is a striking fact that none of the women who were allowed to complete pregnancy died in the follow-up period. That the three patients who died were among those with severe heart disease is indicated by the fact that their pregnancies were interrupted.

A re-evaluation, such as was accomplished in this study, offered a unique opportunity to gather data concerning rheumatic heart disease in women of childbearing age. History, physical examination, and laboratory data all contributed interesting information.

A history of multiple attacks of rheumatic fever was found in 28 patients (13 class I, 7 class II, 7 class III, 1 class IV). In this group of 28, there were 10 interruptions of pregnancy and 12 sterilizations, while in the total group of 106 there were only 16 interruptions. Three of the five patients who had atrial fibrillation in 1950 and 1951 are in this group. These observations indicate that patients with a history of repeated attacks of rheumatic fever tend to develop more severe heart disease and warrant special observation during pregnancy.

The most frequently observed valve lesions, single or combined, found in the patients with rheumatic heart disease, were as follows:

Mitral stenosis and mitral insufficiency	28
Mitral stenosis alone	16
Mitral stenosis, mitral insufficiency, aortic stenosis, and aortic insufficiency	14
Mitral insufficiency	8

Mitral stenosis was the predominant lesion in over 50 per cent of the rheumatic patients.

Of the 71 patients with rheumatic heart disease who reported to the clinic for a complete examination, 16 were noted to have gained or lost murmurs in the past 3 to 5 years. The murmur of mitral stenosis was lost in 4 and gained in 2 cases; that of mitral insufficiency was lost in 2 and gained in 1 case; those of mitral stenosis and mitral insufficiency were lost in one case; that of aortic stenosis was gained in five cases; and murmurs indicating a combination of mitral insufficiency and aortic stenosis were gained in one case. The disappearance of murmurs following delivery may be due to the altered circulatory dynamics of the pregnant state. The murmur that most frequently appeared was that of aortic stenosis, as might be expected in an older group. One of the two patients in whom the murmur of mitral stenosis appeared was in the sixth month of a third pregnancy at the time of the re-examination; the other patient was a 23 year old girl in whom the progression of rheumatic heart disease was apparent in that she showed a concomitant decrease in functional capacity.

Two of the 16 patients who in 1950 to 1951 had signs of, or a past history of, cardiac failure were dead at the time of the re-evaluation. Of the remaining 14 patients with previous failure none has shown progression of heart disease in terms of functional classification. However, only 3 have not been sterilized and only 1 has had a subsequent pregnancy.* Five valvuloplasties were performed on patients who had evidence of cardiac failure in 1950 to 1951; all these were improved but only 2 of the 5 had not been previously sterilized; these patients have not had a subsequent pregnancy. There was no clear evidence of cardiac failure in any of the patients who were re-examined although enlarged, tender livers were palpable in 2 patients.

Atrial fibrillation persisted in all patients who had this rhythm in 1950; of these, 4 are living and 1 is dead. Two patients have developed atrial fibrillation since their previous examinations. Of these 2, 1 had intermittent episodes of atrial fibrillation in 1950, and the other had an undiagnosed arrhythmia during pregnancy.

Not all of the 85 patients who were re-examined had electrocardiograms and full size x-ray films of the chest made during pregnancy. In cases where old tracings and films were available for comparison, there

* This patient was pregnant at the time of examination and was found to have an enlarged tender liver without other clear evidence of cardiac failure or of active rheumatic fever.

was evidence of a change in the electrocardiogram in 10 cases, 3 showing improvement and 7 showing increased electrocardiographic abnormality. Comparison of available x-ray films showed a smaller heart or decreased vascular markings in 9 patients, and a larger heart in 5 patients. There was no apparent relationship between the x-ray and electrocardiographic changes and the changes in functional capacity except in patients who had had valvuloplasty. Here, there was definite correlation.

In the eight patients with congenital heart disease, cardiac catheterization was not performed to assess the nature of the lesions. Probable diagnoses based on available work-up were as follows: interatrial septal defect, 1 patient; subaortic stenosis, 2 patients; pulmonic stenosis, 2 patients; coarctation of the aorta, 3 patients.

Discussion

The course of the 106 cardiac patients who were observed during this study was surprisingly good in regard to both survival and well-being. There were no maternal deaths during pregnancy or in the postpartum period in this group of 106 patients. Three to 5 years after their pregnancies only 3 of the 106 patients were dead. Sixty-five patients (61 per cent) were functionally unchanged according to the American Heart Association Classification, and 27 patients (26 per cent) showed an improvement in their cardiac functional ability. In 5 of these this improvement could be attributed to valvuloplasty and in another to resection for coarctation of the aorta. Only 14 patients (12 per cent) showed progression of heart disease in terms of functional classification.

Because of the small number of patients with congenital heart disease in this study, no conclusions can be drawn as to the effect of pregnancy on congenital heart disease, and the following comments apply to the 92 patients with rheumatic heart disease.

Several explanations may be invoked to explain the relatively benign course of the patients in this study. As has been known since Grant's classic work,[5] the adult patient with valvular heart disease may maintain well-being for many years before the intervention of congestive heart failure. Furthermore, all our patients had already survived to the childbearing age and thus had passed the period of greatest mortality in the natural history of rheumatic fever. According to Wilson,[6] two thirds of the total mortality in children with rheumatic fever occurs before puberty and of those who survive to age 15, over 70 per cent can be expected to survive to age 40. In the study of Bland and Jones[4] of 1,000 patients who survived their first attack of rheumatic fever at an average age of 8 years, 202 were dead at the end of 10 years, and only an additional 99 died in the second 10 years following their initial attack of rheumatic fever. Twenty years after the acute attack, 699 of the original group were alive (380 with rheumatic heart disease) and of these, 3 out of 4 had little or no limitation. Thus, in a real sense, our patients had been selected by the natural history of rheumatic fever as a group with a relatively good prognosis. In addition, in 5 of the patients with severe rheumatic heart disease and in 1 with congenital heart disease (coarctation of the aorta) the natural history of the disease was altered by surgery.

The patients were further selected by the fact that they were well enough to become pregnant and to complete it, except for the 16 who had therapeutic abortion.

In the past, the influence of pregnancy on the natural course of rheumatic heart disease has been studied largely by reviewing the childbearing record in known cardiac patients. Boyer and Nadas,[7] in a careful review of the age at death in nulliparous women in comparison to those who had survived pregnancy, came to the conclusion that women who have borne children do not die sooner than either nulliparous women or males with rheumatic heart disease. Furthermore, according to their studies, even multiple pregnancies could not be held accountable for any reduction in the average age at death. This study wisely excluded patients who had not survived to the end of the reproductive period (age 40) be-

cause some nulliparae died too early to have a chance at pregnancy.

Little follow-up work comparable with that presented here has come to our attention. In the discussion of a paper presented by Carr and Hamilton,[8] Dr. B. P. Watson reported that of 223 patients with heart disease who survived pregnancy, 9 died within 1 year after delivery, 6 died in the second year after delivery and 31 were dead within 10 years of delivery. Naish's attempt[9] to study the remote effects of pregnancy in cardiac patients is largely invalidated by the fact that she was able to report on only 95 of a total of 426 pregnant cardiac patients. Of this group of 95, seen an average of 5 years after pregnancy, 3 were dead and 37 per cent were worse than before pregnancy.

Haig and Gilchrist[10] conducted a follow-up study of 295 women observed during pregnancy from 1 to 10 years previously. The average duration of follow-up is not given. Forty-one women had died since pregnancy, the majority of deaths occurring in those women who were classified as class IV during pregnancy. They felt that the burden of pregnancy was capable of causing congestive heart failure in a woman roughly 5 to 7 years before it would appear in the normal course of events.

The careful studies of Gorenberg and Chesley[11] lead to a more optimistic conclusion. They state "There is nothing to suggest that the heart is damaged by childbearing or that the course of the rheumatic process is thereby accelerated." They examined 260 women 9 to 14 years after delivery. The groups are therefore to some extent not comparable, and this may explain their observation of a higher annual death rate (26.6 per 1000 per year) than was observed in the relatively short follow-up period of the present series (8.0 per 1000 per year). Cardiac surgery, by altering the natural course of rheumatic heart disease, has probably also played a part in lowering the annual mortality in our group.

Valvuloplasty performed since pregnancy has produced impressive results in the five patients in whom it was performed; all had functional improvement. The greatest improvement in the total group of 106 patients was found in three of the patients who had valvuloplasty. This symptomatic improvement was directly correlated in the 2 patients who reported to the clinic with improved x-ray findings, i.e., smaller heart size and decreased pulmonary vascular markings, and a decreased notching of the P waves in the electrocardiogram. These results make it necessary to discard a therapeutic concept prevalent in 1950 and 1951, i.e., that interruption of pregnancy for cardiac indications should automatically be followed by sterilization. Since the functional capacity of cardiac patients may be changed from class IV to class I by operation, this concept is no longer valid. With increasing knowledge and improving methods of therapy the indications for interruption of pregnancy are becoming more limited.

It should be emphasized again that the improvement in functional ability of some of the patients seen in this study may have been due in large part to the fact that their first classification was made during pregnancy, while in the great majority their follow-up evaluation was while nonpregnant. However, nine of the patients re-evaluated were pregnant at the time of the present study. Despite the circulatory burdens of pregnancy[12] 2 of these pregnant patients showed improvement in terms of functional classification, 4 remained unchanged and only 3 showed a lower functional classification during the period of their present pregnancy.

With regard to management as a factor affecting prognosis the following points may be made. A significant fraction of the patients in the medical clinic of the Boston Lying-in Hospital, between one third and one half, are not aware that they have heart disease until the diagnosis is made during the pregnancy. This is partly because they have not been to physicians and partly because the increased cardiac work of pregnancy tends to increase the evidence of valvular heart disease and to make the diagnosis less difficult. There seems to be no doubt, then, that through the Lying-in Hospital a considerable number of women come under systematic medical supervision who otherwise would not have it. We take

great pains in the medical clinic at the Boston Lying-in Hospital to try to arrange for a continuing follow-up for all of our patients with heart disease. They are referred with complete information to a private physician of their own choice or to one of the many competent medical or cardiac clinics in the community. We are impressed with the probability that the education of these patients during the months of pregnancy appears in many to be followed by a more responsible attitude on their part toward their cardiac disease.

Summary

One hundred and six patients have been restudied three and one half to five years (average 4.1 years) after they were observed with pregnancy and heart disease at the Boston Lying-in Hospital. No patient died during pregnancy or the puerperium. Only three have died since; 92 patients have shown either no change or an improvement in functional classification.

This re-evaluation indicated that the altered circulatory dynamics of pregnancy may temporarily decrease functional capacity. However, no permanent change in degree of heart disease could be directly attributed to the pregnancy for which these patients were followed in 1950 to 1951.

Summario in Interlingua

Cento sex patientes esseva restudiate a periodos de inter 3½ e 5 annos (periodo median: 4,1 annos) post que illas habeva essite observate con graviditate e morbo cardiac al Maternitate Boston. Nulle patiente moriva durante graviditate o puerperio. Solmente tres ha morite al tempore del presente studio; 92 ha monstrate un melioration del classification functional o nulle alteration.

Iste re-evalutation indica que le alterate dynamica circulatori del graviditate pote temporarimente reducer le capacitate functional. Tamen, nulle alteration permanente del grado de morbo cardiac poteva esser attribuite directemente al graviditate pro que le patientes esseva sub observation in le annos 1950 a 1951.

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A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Atherosclerosis

By H. ENGELBERG, M.D., R. KUHN, M.D. AND M. STEINMAN, M.D.

Heparin, 200 mg. subcutaneously, was administered twice weekly to a group of 105 patients with known previous myocardial infarction. A comparable control group of 117 individuals received saline placebos. Over a two-year period, there were 21 deaths due to cardiovascular disease in the placebo group, 4 cardiovascular deaths in the heparin group. The observed differences in deaths between the two groups is statistically significant, $p < .01$. The results indicate that heparin, in the dosage and manner administered, retards the progress of atherosclerotic disease in patients with coronary atherosclerosis.

THE state of the circulating lipids has been the subject of intensive study in the past few years. These lipids do not exist in plasma as pure cholesterol, phospholipid or neutral fat but are bound to protein in the form of complex lipoprotein molecules. Lipoproteins form a spectrum of compounds of varying size and density, and contain different proportions of cholesterol, phospholipid, triglycerides and protein. They can be grossly separated into alpha and beta lipoproteins by electrophoretic or chemical technics, and more quantitatively defined by ultracentrifugal analysis into high and low density lipoproteins of varying S_f classes. Precise delineation of plasma lipoproteins is not only valuable in furthering our understanding of fat metabolism, but is clinically important since the circulating lipids are probably the major source of the increased fats found in atherosclerotic vessel walls. Entrappment of infiltrating lipid particles occurs in the arterial wall, which acts as a filter of molecules circulating in the blood. In this process particle size, shape and charge are undoubtedly of importance, and it may well be that changes in the vascular ground substance also play a major role. Thus the straining properties of the vascular wall rather than the varying chemical composition of the lipoprotein complexes affords a rational explanation for the differential etiologic significance in atherosclerosis of the various lipoproteins.[1, 2] In general, the ultracentrifugally defined low density lipoproteins, and the electrophoretically or chemically separated β-lipoproteins, demonstrate a close correlation with clinical coronary atherosclerotic disease, whereas the smaller high density (alpha*) lipoproteins do not. Since all lipoproteins contain cholesterol in varying concentrations, it is apparent that cholesterol levels on the one hand and low density or beta lipoprotein levels on the other are not necessarily parallel.

A body of evidence has been accumulating which suggests that heparin plays a physiologic role in the serum transport phase of fat metabolism. Chargaff and coworkers in 1941[3] noted that heparin possessed the property of altering the characteristics of naturally occurring lipoproteins. In 1943 Hahn[4] found that heparin abolished alimentary lipemia, an observation extended to other species by Weld.[5] Anderson and Fawcett[6] demonstrated that postheparin plasma could clear lipemia in vitro. The lipid alterations involved in the "clearing" or reduction in turbidity of lipemic plasma were clarified by the observation from Gofman's group,[7] with subsequent confirmation[8] that there is a rapid and profound alteration in the blood lipoprotein spectrum, following the administration of heparin. When it is injected into humans or experimental

From the Cedars of Lebanon Hospital, Los Angeles, Calif.

* The precise relationship between high density lipoproteins (ultracentrifugal analysis) and α-lipoproteins (electrophoretic or chemical analysis) has not been defined.

animals whose plasmas contain elevated levels of chylomicrons or of abnormal low density or beta lipoproteins, these components rapidly disappear from the plasma. Subsequent investigation[9] disclosed that a true lipolysis of neutral fat occurs with a splitting off of free fatty acids and glycerol and that this process is associated with a removal of fat from the blood stream.[10, 11] The demonstrations that biologically active heparin is normally present in the blood,[12] that plasma may have clearing activity without the prior injection of heparin[13], and that lipemia increases following the injection of antiheparin agents[14] lend support to the concept that heparin plays a normal role in the interconversion of serum lipoproteins.

Other lines of investigation suggest that a deficiency of endogenous heparin may be one of the primary causes of excessively elevated serum lipids (more specifically of chylomicra, low density lipoproteins, or β-lipoproteins). It has been found in studies of mast cells (the source of heparin in the animal body) in rats and rabbits[15] that rats, which are highly resistant to experimental atherosclerosis resulting from fat feedings, have many more mast cells than rabbits, which are highly susceptible to atherosclerosis. More recently,[16] it was shown that there are significantly less mast cells in humans with extensive atherosclerosis at autopsy than in nonatherosclerotics in the same age groups. Using protamine[17] and toluidine blue[18] titration technics, which are not specific for heparin, slightly decreased amounts of substances which combine with these chemicals were found in the blood of atherosclerotic patients as compared with the blood of normal individuals. Measurements of circulating heparin[19] indicate that there is an inverse relationship between the low density S_f 0–400 lipoproteins and endogenous plasma heparin levels. If these latter results are confirmed by further investigation, it will suggest an analogy between insulin deficiency, abnormal carbohydrate metabolism and diabetes mellitus on the one hand, and heparin deficiency, abnormal serum lipid metabolism and atherosclerosis on the other.

Several investigators have found that the daily injection of adequate amounts of heparin in cholesterol-fat fed experimental animals minimizes the degree of hypercholesterolemia and reduces the extent of subsequent atherosclerosis.[7, 20-22] Unfortunately in humans, conflicting reports as to the efficacy of heparin in the treatment of angina pectoris have diverted attention from the more fundamental biochemical and pathologic studies. Angina is difficult to evaluate at best and therapeutic results can be submerged when the patient group is diluted with placebo reactors. Furthermore, we believe there is a carryover effect for several weeks to months after heparin is stopped which has led to misinterpretation of the results in blind studies, using placebos. However, results in angina are of secondary importance since it is, after all, a symptom of pre-existing disease which may or may not be amenable to therapy. In view of the alteration of circulating lipoproteins in the direction of increased normality after the injection of heparin, it was important to determine the effect of heparin upon the objective manifestations of the progress of atherosclerotic disease in humans.

Various studies have proven that atherosclerosis is the underlying disease process in 85 to 90 per cent of patients who have sustained a myocardial infarction, or who have typical angina pectoris with abnormal electrocardiograms. Such a group, therefore, lends itself well to the evaluation of the effect of long-term therapeutic measures upon the course of atherosclerotic disease.

Material and Methods

Accordingly over 200 patients in the Cardiac Clinic of the Cedars of Lebanon Hospital who had previously had a myocardial infarction, were alternately placed into two groups. A small number of patients with angina of effort and abnormal electrocardiograms were also included in each group. Doubtful cases were rigidly excluded from the study. All patients were thoroughly examined, preliminary electrocardiograms and ballistocardiograms were taken, and blood samples were drawn for cholesterol and ultracentrifugal lipoprotein determinations.* No patients were included who

* The ultracentrifugal analyses were performed at the Donner Laboratory, University of California at Berkeley, through the cooperation of Dr. John Gofman.

ad sustained an acute myocardial infarction within hree months prior to the onset of therapy.

The patients were all told they would receive ijections of a new medication which seemed promis- ig in the therapy of atherosclerosis. One group as given 200 mg. of concentrated aqueous he- arin† (100 mg. or 200 mg. per cc.) subcutaneously wice weekly, and the other received isotonic saline lacebo injections in a similar manner. In all other espects, therapy was identical in the two groups. asodilating drugs were prescribed when needed or angina or claudication and hypertension was reated by the usual methods. Diabetic therapy as supervised in the diabetic clinic. Low fat diets ere not prescribed except when caloric restriction as indicated for obesity, attempts at weight re- luction in these clinic patients were usually un- uccessful. Oral anticoagulant drugs were not used. A fair percentage of the patients in both groups, or their close relatives, were taught to give the injections at home, usually at bedtime.‡ Where this was not feasible, the patients in both groups ame to the clinic for the medication. It was injected slowly in the relatively painless subcutaneous tissue just above or below the posterior iliac crest, using a 25 gage hypodermic needle. One technician gave all the injections in the clinic and was the only person, apart from the authors, who knew whether the patient was receiving heparin or the placebo. This project was not conducted as a blind study, since symptomatic results were not being evaluated and it seemed safer, in view of the anticoagulant action of heparin, for us to know what each patient received.

Several considerations led to the selection of the 200 mg. dose of subcutaneous aqueous heparin twice weekly, although we appreciated the fact that this might not be sufficient for a marked sustained lipoprotein reduction particularly in patients with highly elevated levels. It had previously been found[7] that 200 mg. of repository heparin produced a substantial though temporary drop in the low density lipoproteins. The subcutaneous route was more practical than the intravenous one; it avoided the extremely high peaks of anticoagulant activity and afforded a much more sustained reduction of lipoproteins. Furthermore, subcutaneously adminis- tered concentrated aqueous heparin, which has anti- coagulant and lipoprotein effects similar to intra- muscular repository heparin, is far less painful, less expensive and much easier to administer than the latter. Although injections of 200 mg. of heparin three times weekly would have afforded a greater average lowering of lipoproteins, we were limited by the amount of heparin available to us, and by the consideration that we wanted to minimize the duration of the anticoagulant effect. It had previously been found[23, 24] that therapeutic levels of anticoagulant activity are maintained for an average of 16 to 18 hours after a 200 mg. subcutaneous dose of concentrated aqueous heparin.

The following criteria were adopted at the onset of the study as affording objective evidence of progress of the underlying atherosclerotic process: (1) cardiovascular death; (2) recurrence of myocardial infarction; (3) gangrene of a limb necessitating amputation and (4) a cerebral vascular accident with objective findings of resultant cerebral damage. When patients were hospitalized, the diagnosis of the in-patient attending staff (who did not know whether heparin or the placebo had been given) was accepted as to whether an infarction had occurred or not. Since we could not logically anticipate any effect of heparin therapy on the atherosclerotic process in a few weeks, recurrences during the first month after the onset of treatment in either group were not included in the results.

Table 1 shows the composition of the two groups. The control series is slightly larger since our heparin supply was adequate for only slightly more than 100 patients. The groups were fairly well balanced, although the patients were alternately allocated with no attempt at matching, in order to eliminate bias in the selection. The heparin series was slightly older and heavier and had somewhat more elevated lipid values, whereas there were proportionately more hypertensives and diabetics in the placebo group and a slightly higher average number of previous infarctions per patient. Chi square analysis

TABLE 1. *Analysis of the Composition of the Heparin and Placebo Groups*

	Total No. of Patients	Male	Female	Average Age in Years	Average Weight	Average Cholesterol	Average* A.I.
					lbs.	*mg. %*	
Heparin	105	73	32	62.6 Range 37-79	150	359	99
Placebo	117	81	37	61.7 Range 36-80	148.3	334	96

	No. of Previous Infarcts	Angina Cases	Average No. of Infarcts per Patient	Years from Last Infarct	Hypertensives	Diabetics	Congestive Failure at Onset of Therapy
Heparin	119	12	1.13	3.7	28	23	6
Placebo	145	11	1.24	3.5	35	30	5

The slight discrepancy of the various factors in the two groups are statistically insignificant.

* A.I.—Atherogenic Index

† Generously supplied by Lederle Laboratories, nc. and Darwin Laboratories.

‡ We are indebted to the Los Angeles Visiting Nurses Service for their cooperation in teaching the patients.

TABLE 2. *Analysis of Results*

	Number of Patients	Months of Therapy	Average Months of Therapy per Patient	Cardiovascular Deaths	Corrected Ratio of Deaths	Nonfatal Recurrences	Total of Deaths and Recurrences
Heparin	105	2067 Range 2-27	19.7	4	4	5	9
Placebo	117	2183 Range 1½-25½	18.7	21	19.9	18	39

The observed difference in the proportion of deaths in the two series is statistically significant, $p < .01$.

TABLE 3.—*Complications Encountered in Patients who Received Heparin*

Complications	No. of Patients
Major hemorrhage	3
Minor bleeding	6
Large local hematomata	3
Minor remote ecchymoses	6
Minor traumatic hemorrhage	2
Thrombophlebitis of leg veins	2
Urticaria	3
Lumbar pain	3
Severe asthma	1
Moderate alopecia	4

TABLE 4.—*Examples of Acute Ultracentrifugal Lipoprotein Changes in Two Patients After Subcutaneous Aqueous Heparin*

	S_f 0–12 mg. %	S_f 12–20 mg. %	S_f 20–100 mg. %	S_f 100–400 mg. %	A.I.
Control Pt. O. M.	553	76	101	34	92
12 hrs. after 200 mg. heparin	547	56	31	0	70
Control Pt. R. D.	526	103	137	38	102
23 hrs. after 200 mg. heparin	506	72	85	16	81

These changes are typical of the effect of heparin.

TABLE 5.—*Low Density Serum Lipoprotein Determinations Prior to Therapy and One Year Later*

	S_f 0–12 mg. %	S_f 12–20 mg. %	S_f 20–100 mg. %	S_f 100–400 mg. %	A.I.
7/24/53 Control prior to therapy	412	36	194	234	122
8/27/54 72 hrs. after last dose of heparin	426	52	109	13	73

Patient received 200 mg. heparin twice weekly subcutaneously. This maintained reduction of lipoproteins is not the usual response.

of each of these possibly important factors, however, reveals that these variations were statistically insignificant. It is evident that these were older individuals with elevated serum lipoproteins, a factor perhaps related to the fairly high proportion of diabetics in the study. Although it would have been desirable to classify the severity of the previous infarction, we were unable to do so as adequate information was not available in many of the patients. However, we believe the extent and severity of the prior episodes of myocardial infarction were comparable in both series.

RESULTS

Table 2 summarizes the results of the two-year study. In the placebo group there were 18 nonfatal recurrences (14 myocardial infarctions, 3 cerebral episodes, and 1 leg amputation for gangrene) and 21 cardiovascular deaths (2 following known cerebral accidents, 2 in congestive failure and 17 after an acute infarction or just sudden death). Thus the death rate in the control patients was approximately 10 per cent per year, which is in keeping with the anticipated yearly mortality in any large group of elderly patients with coronary heart disease. In this group, the recurrences and deaths occurred fairly regularly throughout the period of the study.

In the heparin group, there were 5 nonfatal recurrences (three acute myocardial infarctions and two minor cerebral episodes) and four cardiovascular deaths. The recurrences occurred after 7, 10, 13, 18 and 19 months of therapy and the fatalities after 2, 4, 19 and 21 months. Postmortem examination in 3 of these 4 patients revealed old and recent myocardial infarction in two, and an old but no recent infarct in the third case. No autopsy was obtained in the fourth patient who collapsed and died while at work. There were no known cerebral deaths, and no fatalities due to severe congestive failure without recent acute infarction in the patients who received heparin. The death rate in this group was 2 to 2.5 per cent per year.

In our opinion the number of cardiovascular deaths is the most reliable index for evaluation since the diagnosis is beyond question. Statistically, using the figures for deaths and total patient months of therapy, the observed differences in proportions of deaths between the two series is 3.3 times the standard error of

the difference in proportions or $p < .01$. If the χ square test is applied, using total deaths and number of patients (and disregarding the fact that the patients receiving heparin had slightly more months of therapy per patient), p is between 0.01 and 0.001. Thus, using either calculation, the difference in deaths is statistically significant.

Since to our knowledge, this is the first instance in which fairly large doses of heparin have been given intermittently for several years in a sizeable number of patients, the symptomatic response was carefully recorded. Although for reasons of safety, blind study technics were not employed, the patients' observations were of interest to us.

As is usually noted, 25 to 35 per cent of the control group reported decreased symptoms on placebo therapy, but the favorable response gradually decreased in some patients. Symptomatic improvement occurred in 50 to 75 per cent of the patients who received heparin and was usually fairly well maintained. We also noted that most often, in contrast to the placebo patients, there was slowly progressive improvement for several months in the heparin group. The patients reported improvement in headaches, vertigo, tinnitus, angina, dyspnea, hip and thigh pain, claudication, weak spells and fatigue, all of which may be symptoms of widespread atherosclerosis. A generally improved sense of well being with an increased effort tolerance was the usual response after several months of heparin therapy.

Table 3 shows the complications that were encountered in the heparin group, other than minor ecchymoses at the site of injection which occurred occasionally in most of the patients and were insignificant. There were three instances of major hemorrhage; two were intestinal and one was renal. X-ray study revealed adenocarcinoma of the stomach in one patient and a kidney stone in another. Thus, there was only one instance of major hemorrhage that was apparently due to the heparin itself and in this patient the drug was not continued. There were no hemorrhagic fatalities. There were six minor episodes of bleeding: one nasal, four rectal and one pulmonary. All the rectal cases had had previous hemorrhoidal bleeding and the patient with bloody sputum had known bronchiectasis. Heparin was successfully continued in all, except in the patient with bronchiectasis where further therapy was not given as bleeding occurred after each injection. There were two instances of post-traumatic minor hemorrhage: one followed a tongue bite incurred while chewing, and the other occurred when a small rectal abscess was mistakenly incised one hour after an injection of heparin. During the entire study intravenous protamine sulfate* was used three times for bleeding and was very efficacious. There were only three instances of large, painful hematomata at the site of injection. The use of small needles and a slow speed of injection were important factors in minimizing the occurrence of local ecchymoses. Six patients complained of an increase in discrete ecchymotic spots remote from the injection site. All were given oral P factor therapy† for several months which was helpful. Thrombophlebitis of the leg veins occurred in two patients while on heparin therapy, perhaps related to a rebound effect. One of these patients had a nonfatal pulmonary infarct and refused to continue the heparin. He was then dropped from the study and was subsequently uneventfully maintained on oral anticoagulants. In the other patient heparin was subsequently successfully continued in 150 mg. doses three times weekly in order to decrease the interval between injections and so possibly decrease any rebound effect. Three patients had lumbar pain and three had urticaria following each dose of heparin. All six had relief from these complaints, when colorless heparin was used instead of light brown material, indicating that these symptoms were not due to heparin itself. One patient had a severe asthmatic reaction after every heparin injection regardless of the color of the material and was forced to discontinue therapy despite the concomitant use of antihistamine drugs. In four patients a mild-moderate alopecia occurred.

In all, heparin therapy was stopped in four cases because of complications. It has been our

* Kindly supplied by Dr. K. Kohlstadt of Eli Lilly and Co.

† Kindly supplied as Cepevit by Wynlit Pharmaceuticals, and as C. V. P. capsules by U. S. Vitamin Corporation.

experience that hemorrhagic complications are infrequent, usually minor, and rarely demand cessation of therapy. If major hemorrhage occurs, a diligent search should be made for some other factor initiating the bleeding which is then intensified by the anticoagulant action of heparin.

Various other problems arose during the study which are worthy of discussion. Chronic duodenal ulcers were present in six of our heparin patients. Therapy was not withheld and no hemorrhage occurred in these cases. Antacid therapy was maintained in all. The presence of severe hypertension apparently added little danger to heparin therapy despite the hazard of vascular rupture. There were only two minor cerebral incidents during heparin therapy, and only one of these was in a hypertensive patient, whereas there were four cerebral accidents in hypertensive patients in the placebo series. When surgery was necessary, no heparin was given in the 48 hours prior to operation and no increased bleeding was noted at surgery. There were five major surgical procedures in the heparin group with no cardiovascular complications in the operative, postoperative or convalescent periods. There were six instances of major surgery in the control group with one episode of nonfatal acute myocardial infarction on the fourth postoperative day. Some of the patients with congestive heart failure reported a decrease in the need for mercurial diuretics, although no additional measures for decompensation were used other than those previously prescribed. This impression of improvement in congestive failure is borne out by the fact that in the heparin group none of the six patients with obvious heart failure at the onset of therapy died during the study, whereas in the control group, of the five patients with obvious failure at the onset of therapy, two subsequently died. In some of the elderly diabetics we again verified an earlier observation[25] that insulin requirements may be decreased 10 to 20 units when heparin is given. One elderly diabetic woman on insulin, who had severe angina and a previous infarction, died suddenly one hour after her second injection of heparin. While the cause of death was not proven, it may be that a hypoglycemic reaction, which is known to be dangerous in the presence of coronary disease, precipitated a fatal cardiac incident in this patient. In view of this occurrence and other observations of decreased glycosuria and an increase in the frequency of mild hypoglycemic reactions when heparin is given to diabetics who are taking insulin, it is wise to reduce the dose of insulin by 15 to 20 units on the day heparin is started. The insulin dosage can be subsequently increased if necessary.

The prolonged administration of intermittent heparin injections has afforded the opportunity to observe the effects upon coagulation and lipoproteins. Three-tube Lee-White clotting times were determined after the first year of therapy in all the patients. Prolongation of the clotting time beyond an average of 16 to 18 hours (range 12 to 26 hours) was observed in only a few instances, perhaps 5 to 10 per cent of the patients. There is apparently very little tendency, in the dosage schedule we used, for a cumulative heparin effect sufficient to result in maintained therapeutic anticoagulation. Thus clotting time determinations are superfluous, when heparin is given subcutaneously in 200 mg. doses twice weekly to patients who do not have severe liver disease.

Table 4 shows two typical examples of the changes in the S_f 0–400 low density lipoproteins 12 and 23 hours after a 200 mg. subcutaneous injection of concentrated aqueous heparin. In some patients, these lipoproteins are back to control levels within 24 hours, in others the effect is more prolonged. Unfortunately, we only have lipoprotein determinations in a small percentage of the patients after 6 to 18 months of heparin therapy. In most of these the serum lipoprotein levels 48 hours after the previous dose of heparin were approximately the same as prior to the onset of therapy. In a few however, the low density lipoproteins, determined 48 to 72 hours after the last dose of heparin so as to avoid its acute effects, were considerably below control levels (table 5). It appears that in a minority of the patients, there is a marked sustained reduction in the average level of low density lipoproteins (on the dosage schedule administered), whereas the majority have only a temporary (24 to 36

hour) decrease following each injection of heparin. Cholesterol levels are variable in the 24 hours after 200 mg. of heparin is given subcutaneously and show relatively little change (perhaps a slight reduction in some instances), when determined after 6 to 18 months of therapy.

Discussion

In view of the multiplicity of actions of heparin and the numerous factors which may play a role in the progress of atherosclerotic disease, it is difficult to assess accurately the differential role of the various mechanisms through which heparin produced the beneficial effects noted in this study. As previously stated a therapeutic anticoagulant level persists for an average of 16 to 18 hours following a 200 mg. subcutaneous dose of concentrated aqueous heparin. Unless undetectable clinical levels of anticoagulant activity persist and are beneficial, a concept for which there is no evidence at all, it is unlikely that therapeutic anticoagulation for 12 to 24 hours twice a week is alone responsible for our results. It may have been an important factor. The prolonged use of anticoagulant drugs reduces the incidence of recurrences and death in patients with previous myocardial infarction, but the results reported [26, 27, 28] are not as good as those we obtained using intermittent heparin therapy which afforded therapeutic anticoagulation only 20 to 30 per cent of the time.

Since elevated serum lipids and lipoproteins are an important factor in atherogenesis and since heparin lowers the low density lipoproteins and accelerates the removal of fat from the blood stream, we believe this action of heparin is probably primarily responsible for the differences in deaths we have observed. We have insufficient observations to determine accurately the average lowering of lipoproteins in our patients, a matter which would have necessitated many ultracentrifugal analyses per patient. However as table 4 illustrates, there was an average overall reduction in the low density lipoproteins, although the effect of each injection was temporary. This reduction itself is important in retarding the rate of progression of atherosclerotic disease although its quantitative contribution[1] is difficult to assess exactly.

The decrease in low density or β-lipoproteins following heparin may be advantageous apart from the average lowering of the lipoprotein concentrations. In all studies of the infiltration of vascular walls by lipids, time is an important factor.[29, 30] Thus, since the injection of heparin is followed by a marked though temporary reduction of the low density lipoproteins, a considerable interval may elapse after the concentration of the circulating lipoproteins has regained its preheparin levels before substantial amounts of lipid again penetrate into the arterial walls. Furthermore, macromolecules form films[31, 32] upon the surfaces of the cells and the vascular intima. These films probably interfere to some extent with the normal molecular exchange between the plasma and interstitial fluid. Martin and Hueper[33] found a decreased rate of oxygen uptake by erythrocytes in hypercholesterolemic rabbits, and we[34] recently demonstrated increased arteriovenous oxygen differences (apparently the result of increased tissue oxygen consumption) after the injection of heparin in atherosclerotic patients. The largest lipoproteins, because of their decreased ability to escape through the capillary pores, would be most likely to form fat sludges on the endothelium. Since it is precisely these larger fat particles which almost disappear, following an adequate dose of heparin (table 4), the harmful effects of intimal films would be substantially ameliorated by heparin therapy. Reformation of films almost certainly would take longer than the simple reaccumulation of circulating lipoproteins. Finally, the beta lipoproteins have been found to interfere with glucose uptake by the diaphragm.[35] Thus, their lowered concentration following heparin may permit more normal carbohydrate metabolism, particularly in diabetics.

Heparin may also be of value in retarding cardiovascular degeneration in atherosclerotic patients because of its affinity for the intercellular cement substance. In a recent study of venous endothelium,[36] it was found that adherence of platelets to the endothelial surface was the initial occurrence following various types of injury and that heparin was effective

in preventing the deposition and agglutination of the platelets on the intercellular cement. Since this platelet agglutination on the cement substance may well be one of the initiating steps in thrombosis, heparin may be valuable at this site apart from its general anticoagulant action. Various workers[37, 38] believe that minute mural thrombosis plays a part in the development of atherosclerosis entirely apart from its role in the formation of large clots.

There are other known actions of heparin which could be commented upon, such as its marked inhibitory effect in experimental pulmonary edema,[39] but the mechanisms already discussed appear to be those most apt to have been involved. Further speculation would add little. Perhaps of greater practical importance is the demonstration of how safely heparin can be used in this manner for years. This requires re-emphasis since there is a justified concern about the risks involved in the use of continuous oral anticoagulant therapy, particularly where excellent laboratory controls are not easily available. Intermittent heparin therapy does not produce a maintained anticoagulant effect and, therefore, no laboratory tests are required. It should not be given in the presence of active bleeding or of severe liver disease, but we have observed no particular danger when it is used in patients with chronic duodenal ulcers, hypertension, hemorrhoids or other possible minor sources of bleeding. If hemorrhage should occur, it can be easily and quickly controlled by the injection of protamine sulfate intravenously, or by blood transfusion. In two years we observed only one major hemorrhage, apparently due to the heparin itself, and no hemorrhagic fatalities, although over 17,000 injections of 200 mg. of heparin were administered. The markedly reduced incidence of recurrent coronary thrombosis as compared with the control group attests to the fact that the theoretic danger of intimal capillary hemorrhage initiating a thrombus has no practical significance.

Other modalities have been successfully used in attempts to reduce the rate of recurrence and death in patients with known coronary disease. The results reported have not been as good as those we have obtained. Morrison[40] found a reduction in mortality over a three year period from 10 per cent per year in his control group to 4.7 per cent per year in his patients on a rigid (25 Gm.) low fat diet, a ratio of slightly better than 2:1. However, most patients will not strictly adhere to a low fat diet, and in our experience the diet alone does not effectively reduce serum lipids and lipoproteins in all instances. The prolonged use of oral anticoagulants has also been reported [26-28] to reduce the incidence of recurrences and death in approximately a 2:1 or 3:1 ratio. However, the incidence of major hemorrhage in these series was not small, even with good laboratory controls. Moreover, since the prothrombin depressing drugs do not have any effect upon serum lipoproteins, it is probable that although they reduce the occurrences of thrombotic incidents, they retard the basic atheromatous process very little if at all.[26] Estrogens have recently been advocated since they reduce the concentration of the β-lipoproteins. However, the large doses required produce such severe feminizing side effects that this form of therapy is most distressing, psychologically traumatic and impractical,[41, 42] except in a very few instances. The other so-called lipotropic agents thus far available, such as various choline and inositol combinations, have little evidence to justify their use.

Objections to the administration of heparin in advanced human atherosclerotic disease are imposed by its cost, the fact that it must be taken by injection and that it apparently should be indefinitely continued. The analogy to the use of insulin in diabetes mellitus is apparent. Pursuing this analogy a step further, it may be that where diet, or perhaps thyroid in hypothyroid patients[43] markedly reduces the low density or β-lipoproteins, the use of heparin is unnecessary. Where the diet is intolerable or where the serum lipids are only moderately reduced thereby, our results indicate that heparin should be given. Although heparin alone was prescribed for our patients without restriction of fats or cholesterol, it appears logical that the combination of moderate fat restriction (which is not too difficult) plus heparin should give better results than the use of heparin by itself. We

do not know if different heparin schedules, such as small daily doses, would be more advisable than the one used in this study, or whether other routes would be preferable. Administration of heparin three times a week would seem to be indicated where there is evidence of complications due to a rebound effect, where the serum lipoproteins are excessively elevated or, for a short time, if anginal symptoms are increased for any reason.

The reduction in mortality in this elderly group of coronary patients, to 2 to 2.5 per cent per year during the first two years of heparin therapy, affords evidence once again that atherosclerosis is not an inevitable consequence of aging, but that it is a disease process at least partially amenable to prevention. Further advances in therapy will undoubtedly keep pace with increasing knowledge of its etiology and pathogenesis.

Summary

(1) The effect of prolonged, intermittent heparin therapy has been evaluated during the past two years in a large number of patients who had previously sustained a myocardial infarction.

(2) There were four deaths due to cardiovascular disease in a group of 105 patients (average age 62.6 years) who received 2067 months of heparin therapy (200 mg. concentrated aqueous heparin given subcutaneously twice weekly).

(3) In a comparable control group of 117 individuals (average age 61.7 years) who received 2183 months of placebo therapy there were 21 deaths due to cardiovascular disease.

(4) The observed difference in deaths between the two groups is statistically significant ($p < .01$).

(5) When heparin is given as described, therapeutic anticoagulant levels are not maintained. Clotting time tests are, therefore, unnecessary.

Summario in Interlingua

(1) In le curso del passate duo annos, le effecto de un prolongate intermittente therapia a heparina esseva evalutate in un grande numero de patientes qui habeva previemente suffrite un infarcimento myocardial.

(2) Occurreva 4 mortes debite a morbo cardiovascular in un gruppo de 105 patientes (etate median: 62,6 annos), qui recipeva un total de 2067 menses de therapia a heparina (200 mg de concentrate heparina aquose administrate subcutaneemente duo vices per septimana).

(3) In un comparabile gruppo de controlo de 117 individuos (etate median: 61,7 annos), qui recipeva un total de 2183 menses de therapia a medication fictive, il occurreva 21 mortes debite a morbo cardiovascular.

(4) Le observate differentia del mortes in le duo gruppos es statisticamente significative ($p < .01$).

(5) Le supra-describite maniera de administrar heparina non resulta in un mantenentia de therapeutic nivellos anticoagulante. Tests del tempore de coagulation es consequentemente innecessari.

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The Persistent Ostium Primum Atrial Septal Defect

By S. Gilbert Blount, Jr., M.D., Oscar J. Balchum, M.D., Ph.D. and Goffredo Gensini, M.D.

Five patients with an ostium primum type of atrial septal defect were studied by clinical and laboratory methods and the diagnosis was verified either at the time of open-heart surgery and/or at autopsy. The atrioventricular valves formed the floor of the defect and were deformed in 4 of the 5 patients. Mitral insufficiency was present as a result of this valvular deformity in these four patients. This valvular deformity resulted in a high pitched blowing systolic murmur, audible over the apical and lower left sternal areas, and left axis deviation and indications of left ventricular hypertrophy, determined by electrocardiography. The deformity of the mitral valve is considered to be the basis for these variations from the typical findings found in the patient with an ostium secundum type of atrial septal defect and make the differential diagnosis of the persistent ostium primum possible under these circumstances.

RECENT developments in the surgical therapy of congenital heart disease include the closure of atrial septal defects by various techniques, the method employed at this institution consisting of suture closure under direct-vision, open-heart surgery.[1, 2] The more frequent centrally located ostium secundum type of defect usually offers little technical difficulty to complete closure.[3-5, 7, 9-11] The situation unfortunately differs greatly in the presence of the ostium primum type of atrial septal defect.[4, 5] Thus it is imperative and of more than academic interest to anticipate prior to surgery the type of atrial septal defect that may be encountered.

There are several factors that readily account for the difference in ease of technical closure and that determine the success and ultimate outcome of the procedure. Atrial septal defects of the so-called primum type are usually associated with abnormalities of varying degree of the atrioventricular valves. This is secondary to the maldevelopment of the embryonic common atrioventricular canal. All gradations of involvement are possible from the common atrioventricular valve with patency of the upper portion of the ventricular septum to minor involvement of either the mitral or tricuspid valves with the ventricular septum remaining intact. Realization of the presence of these defects of the atrioventricular valves and of the ventricular septum makes the technical difficulties to closure readily appreciated. Review of the literature has not revealed any information relative to this differential diagnosis.

A group of 85 patients with atrial septal defects have been studied at this institution during the past four years. The ostium primum type of defect has been established in five of these patients, either at operation or at postmortem examination. While it is realized that no single finding is definitely diagnostic of a persistent ostium primum, certain distinctive features are apparent and a review of these findings has led to the belief that the ostium primum type defect can frequently be distinguished from the ostium secundum type defect. Postmortem examination or direct inspection of the atrial septum at the time of open heart surgery together with an evaluation of the adequacy of valvular function at operation has offered the opportunity of correlating the clinical findings with the anatomic features in the individual case.

It is the intent of this communication, there-

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fore, to review the findings upon which this differential diagnosis is based.

Embryology

At an early stage in the development of the heart the common atrium is separated from the common ventricle by a constricted passage termed the atrioventricular canal.[6] The septum primum first appears from the superior-posterior aspect of the common atrium, growing caudally to reach the atrioventricular cushions. The latter are protuberances forming on the anterior and posterior walls of the atrioventricular canal, which fuse to divide this canal into right and left atrioventricular canals. These cushions form the septal cusps of the mitral and tricuspid valves, and a portion of the upper part of the interventricular septum. The remainder of the interventricular septum develops from the lower part of the common ventricle and extends upward to meet and fuse with the atrioventricular cushions. The septum primum joins with the fused atrioventricular cushions, forming the right and left atria. Normally this fusion is complete and the upper portion of the septum primum undergoes degeneration, just prior to its union with the fused atrioventricular cushions; an opening called the ostium secundum results. The septum secundum starts to form from the wall of the right atrium between the septum primum and the entrance of the superior vena cava and grows downward until its lower edge overlaps the foramen secundum. The passage thus formed between the two atria is termed the foramen ovale, and is bounded by the lower part of the septum primum below and the inferior border of the septum secundum above.

Failure of the septum primum to join with the fused atrioventricular cushions leaves an opening, the persistent ostium primum. This defect is usually large and is often accompanied by abnormalities in the development of the endocardial cushions resulting in associated malformations of the mitral and tricuspid valves and at times a defect of the upper portion of the ventricular septum. The mitral valve is more frequently involved than the tricuspid.

Material

Five patients with an ostium primum type of atrial septal defect were selected from a group of 85 patients with atrial septal defects which have been studied by clinical and laboratory methods, including cardiac catheterization. The size and location of the defect and the status of the atrioventricular valves were determined at the time of direct-vision, open-heart surgery in two patients and at postmortem examination in three patients. The age of these patients ranged from 27 months to 10 years. A summary of the history and clinical findings is as follows:

Case 1. S. A., was a 4 year old boy. The mother's pregnancy was without incident and the patient was the product of a normal delivery with a birth weight of 6 pounds and 7 ounces. Development was normal, although he was always small for his age. He was an active child but tired easily with prolonged exertion. There was no definite history of frequent upper or lower respiratory infections. A heart murmur was first detected at the time of a routine physical examination at the age of 4 years.

The physical examination revealed that the neck veins were not distended nor pulsating. There was a slight prominence of the precordium, and upon palpation a hyperactivity of the heart was detected along the lower left sternal border. No shocks nor thrills were palpable, but percussion revealed the heart to be definitely enlarged to the left. Auscultation over the second intercostal space at the left sternal border revealed that the second heart sound was accentuated and moderately reduplicated. A loud (grade 3 on a grade 6 basis) rough systolic murmur was heard over the entire precordium and posteriorly over the left lung base, of maximal intensity in the second interspace at the left sternal border. A low-pitched mid-diastolic murmur was audible in the area just to the left of the lower sternum. The lungs were clear and there was no cyanosis, clubbing nor peripheral edema and the femoral pulsations were within normal limits. Neither the liver nor spleen were palpable.

At operation a large right atrium and right ventricle were found. The atrial septum was practically nonexistent, with only a slight ridge being present superiorly and posteriorly.

At postmortem examination (fig. 5*A*) there was a large defect in the lower portion of the atrial septum. The mitral and tricuspid valves were deformed. The aortic leaflet of the mitral valve and the medial leaflet of the tricuspid valve were divided into two parts by a continuous cleft. The medial leaflet of the tricuspid valve had a larger (two-thirds) posterior and a smaller (one-third) anterior segment. The lat-

ter was devoid of chordae tendineae and formed a ruffled fold. The aortic leaflet of the mitral valve was divided into a large (two-thirds) anterior and a smaller (one-third) posterior segment. The chordae tendineae of the latter segment were attached to the adjacent endocardium and not to the papillary muscles. The anterior portion of the aortic leaflet of the mitral valve and the medial leaflet of the tricuspid valve were continuous across the floor of the atrial septal defect. All of the leaflets of the mitral and tricuspid valves had flattened irregular gray-white nodules near their free ends, which measured up to 4 mm. in diameter. The pulmonary veins entered the left atrium in a normal manner.

Case 2. R. L., was a 27 month old boy. The mother's pregnancy and delivery were normal. The infant's birth weight was five pounds and five ounces. Development and weight gain were poor, and he experienced frequent upper and lower respiratory infections. Breathing was labored and dyspnea was manifest upon mild exertion. A heart murmur was first noted upon routine physical examination at the age of 4 months. The patient was in failure at this time and was digitalized. The physical examination revealed a slight bulging of the precordium with an excessively forceful beating of the heart being felt along the lower left sternal border. A shock was palpable in the second intercostal space at the left sternal border, and a thrill was present in the fourth intercostal space extending from the sternal border toward the apex. The heart was enlarged to percussion, its margin extending to the left anterior axillary line. Auscultation revealed that the second sound in the second left intercostal space was greatly accentuated and definitely reduplicated. A grade 4 rough blowing systolic murmur was audible over the entire precordium, and was of maximum intensity in the fourth intercostal space at the left sternal border, and was louder in the fifth than in the second intercostal space. A separate higher pitched systolic murmur was audible over the apical area. A gallop rhythm was present, due to the presence of a low pitched mid-diastolic murmur which was audible along the lower left sternal border and also over the apical area. Neither cyanosis nor clubbing was noted. Peripheral edema was not detected, but the liver edge was palpable 4 cm. below the right costal margin, although no rales were audible. The femoral pulsations were normal in amplitude.

The right atrium, right ventricle and pulmonary artery were found to be markedly enlarged at the time of operation. A systolic thrill was palpable over the right atrium. A low atrial septal defect of the ostium primum type was estimated to measure 3 by 2 cm.

Postmortem examination revealed that both ventricles were markedly enlarged, the right more than the left. The right atrium was greatly dilated while the left atrium was small. A large defect was present in the inferior central portion of the atrial septum, with the atrioventricular valves forming the floor of the defect. The medial tricuspid leaflet was short and bound down to the ventricular septum. The other leaflets were broadened, and the chordae tendineae were thickened and short. The line of attachment of the posterior leaflet of the mitral valve was short and blended into the inferior border of the atrial septal defect. A broadened commissure was present between the anterior and posterior leaflets. The anterior leaflet was normal. Several chordae tendineae extended from the anterior papillary muscle to the superior portion of the ventricular septum, and were thicker and shorter than normal.

Case 3. E. B., was a 10 year old boy. The mother's pregnancy was without incident, and he was the product of a normal full-term delivery. The birth weight was 7 pounds and 8 ounces. His physical development was apparently normal, although he was mentally retarded. He began having epileptiform attacks during an episode of whooping cough at the age of one and one-half years, and a heart murmer was first heard at this time. There was no definite history of upper or lower respiratory infections. He was always active and vigorous, without limitation of exercise tolerance.

The physical examination revealed that the chest was symmetrical. A forceful beating of the heart was noted along the left lower sternum, and a thrust was palpable in the second left intercostal space. There were no thrills nor shocks palpable. The heart was enlarged upon percussion, its border extending to 1 cm. beyond the left mid-clavicular line. Auscultation revealed that the second sound in the second left intercostal space was slightly increased in intensity and widely reduplicated. A grade 3 rough systolic murmur was audible over the anterior chest and was of maximum intensity in the second left intercostal space at the sternal margin. A prominent low-pitched mid-diastolic murmur was audible in the region between the lower sternum and the apex of the heart. There was no cyanosis, clubbing of the digits nor peripheral edema, and the liver was not palpable. The femoral pulsations were of normal amplitude.

This patient succumbed during an epileptiform seizure which occurred on the day prior to operation.

Necropsy revealed the right atrium and right ventricle to be greatly enlarged (fig. 5, *B*). An atrial septal defect was present resulting in a roughly elliptical opening which was 3 cm. long by 2 cm. wide and located in the lower portion of the atrial septum immediately above the atrioventricular valves. The foramen ovale was anatomically patent. The atrioventricular valves were normal.

Case 4. J. R. was a 4 year old boy. The mother's pregnancy and delivery were normal. Birth weight was 7 pounds and 5 ounces. Development was normal, although growth was slow. At the end of one

year he weighed only 17 pounds. There were frequent and prolonged upper respiratory infections. Dyspnea and fatigue were manifest on slight exertion. The presence of a heart murmur and cardiac enlargement were first detected at 1 year of age.

Inspection revealed definite prominence and hyperactivity of the precordium. No thrills were palpable, but a faint shock was present in the second left intercostal space. Percussion revealed the heart to be enlarged to the left anterior axillary line. The point of maximum impulse was diffuse and palpable in the fifth and sixth intercostal spaces. Auscultation revealed the second sound in the second left intercostal space to be greatly increased in intensity and slightly reduplicated. A grade 3 to 4 harsh, systolic murmur was audible along the left sternal border, and a systolic murmur of a slightly higher-pitched quality was heard in the region of the fourth intercostal space at the left sternal border. A short low-pitched mid-diastolic murmur was audible over the apical area. There was no cyanosis nor clubbing of the digits. Peripheral edema was not present, the liver was not palpable, and the lungs were clear. The femoral pulsations were of normal amplitude.

The right atrium and right ventricle were greatly enlarged at operation. The left atrium appeared to be normal in size. The pulmonary artery was twice the size of the aorta. A thrill was palpable over the posterior portion of the right atrium. No septum could be palpated by finger exploration of the interior of the right atrium. When the exploring finger was inserted through the atrial defect a regurgitant jet through the mitral valve was felt, indicating mitral insufficiency. No attempt at closure was made.

Case 5. M. O'C., was a 28 month old girl. The mother's pregnancy was normal and the patient was the product of a normal full-term delivery. Her birth weight was 5 pounds and 9 ounces. Development and weight gain were poor and she suffered many upper and lower respiratory infections, including three episodes of pneumonia. She was very active, but experienced fatigue and dyspnea with exertion. Enlargement of the heart, cardiac murmurs and heart failure were first detected at the time of hospitalization for pneumonia at the age of 14 months.

Physical examination revealed prominence and hyperactivity of the precordium. There was a sustained thrust between the left lower sternum and the midclavicular line. A faint shock was palpable in the second left intercostal space at the left sternal border, but no thrills were present. Percussion revealed the heart to be enlarged to the left anterior axillary line. Upon auscultation the second heart sound in the second intercostal space at the left sternal border was widely reduplicated and increased in intensity. A soft blowing grade 2 to 3 systolic murmur was audible at the base of the heart, which was of maximum intensity in the second left intercostal space and well transmitted toward the shoulders. There was in addition a high-pitched blowing systolic murmur, grade 3 to 4 in intensity, audible over the apical area and transmitted toward the axilla. A short, low-pitched murmur was heard in early diastole, being of maximum intensity over the lower left parasternal area. No cyanosis, clubbing of the digits, nor peripheral edema was present, and no rales were audible over the posterior chest. The femoral pulsations were of normal amplitude.

Palpation of the exposed heart at the time of operation revealed a thrill to be present over the posterior portion of the right atrium and the pulmonary artery. A definite regurgitant jet was felt by the exploring finger when it was passed through the defect to the area of the mitral valve, indicating definite mitral insufficiency. Inspection revealed the atrial septum to consist of only a narrow rim in the superior and posterior portion of the atrium.

Discussion

History. The history of these five patients revealed that their birth weights were normal, but that growth and development were retarded. Upper and lower respiratory infections were a prominent feature of their history and the exercise tolerance was significantly decreased with the development of congestive failure in three patients. Therefore the history and symptomatology present in the patient with an ostium primum type of atrial septal defect are in general similar to those of the patient with an ostium secundum defect, and are the symptoms of patients with large left to right shunting of blood.

Their symptoms, however, are manifested earlier in life and are in general more incapacitating.

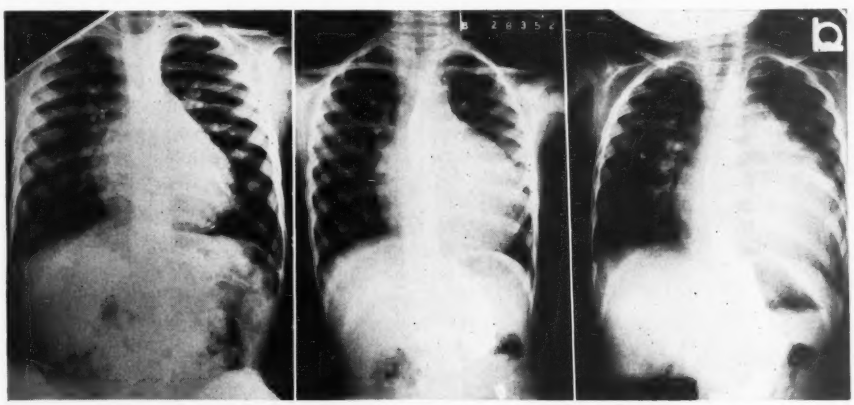
The increased severity of these symptoms is considered to reflect the larger volume of left to right blood flow which frequently occurs in these patients. The insufficiency of the atrioventricular valves also contributes to the increased work of the heart in the patient with a persistent ostium primum defect.

Physical Examination. The physical findings likewise resembled those of patients with the ostium secundum type of atrial septal defect. However, there were additional features of the cardiac examination which led to the consideration of the diagnosis of an ostium primum defect.

The first group of findings is considered to reflect the greater derangement of the hemodynamic pattern present in this defect. The heart was usually of greater size as reflected by the bulging precordium and other physical signs of cardiomegaly. The systolic murmur was of greater intensity, rougher in quality, and more widely transmitted than the murmur usually present in the patient with a secundum type of defect. This is the result of the greater degree of functional stenosis secondary to the higher pulmonary flows frequently found in patients with this type of defect. The second heart sound, audible in the second left intercostal space, tended to be louder in these patients and a palpable shock was present in this area in three of the five patients. This sound was reduplicated in all patients but widely split in only two patients. This contrasts with the patient with a secundum type defect where the primary feature of the second heart sound is the reduplication and not the intensity. The increased intensity of the second heart sound is considered to reflect the greater pulmonary flow and pressure frequently present in patients with the ostium primum type of defect. The constant mid-diastolic murmur present over the tricuspid area in these patients results from the high volume of flow across the tricuspid valve and the resulting functional tricuspid stenosis. It is again emphasized that this murmur does not necessarily indicate organic stenosis of the mitral valve as the mitral orifice was not narrowed in any patient in this group.[3]

The second important finding that should lead to the suspicion of the presence of an ostium primum type defect is the systolic murmur located at the apical area and/or along the lower left sternal border. This murmur has a high pitched blowing quality, and is frequently loud and widely transmitted. The presence of this murmur suggests an ostium primum type of defect and is considered to be due to the malformation and resulting insufficiency of the mitral and/or tricuspid valves.

Fluoroscopy. The fluoroscopic examination revealed the vascularity of the peripheral lung fields to be greatly increased. The main pulmonary artery and the right and left pulmonary arteries were enlarged and the amplitude of their pulsations was increased (figs. 1 and 2). The aorta was inconspicuous in these patients. The heart was considerably to markedly enlarged in all patients and in general the overall heart size was greater than the heart size of patients of this same age group having a secundum defect. The right atrium and the right ventricle were markedly enlarged. This enlargement of the right ventricle is mainly the result of dilatation and therefore the true size of the main pulmonary artery is frequently underestimated due to the dilatation of the outflow tract of the right



A *B* *C*

FIG. 1. Postero-anterior roentgenograms of (*A*) patient S. A., case 1, (*B*) patient R. L., case 2 and (*C*) patient J. R., case 4.

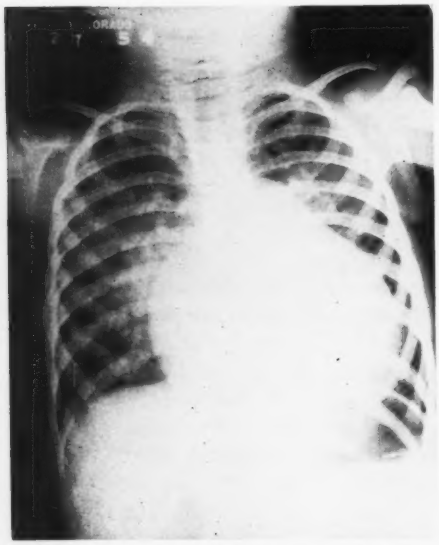


FIG. 2. Postero-anterior roentgenogram of patient M. O'C., case 5.

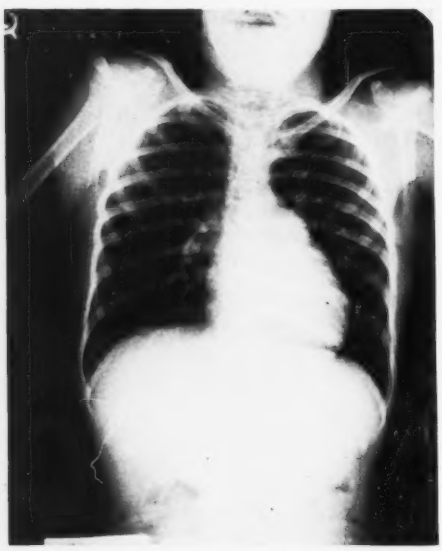


FIG. 3. Postero-anterior roentgenogram of Patient E. B., case 3.

ventricle. The detection of differential chamber enlargement is often difficult if not impossible in the presence of marked cardiac enlargement; nevertheless, there was suggestive evidence of enlargement of the left ventricle in four of the five patients. This enlargement of the left ventricle is considered to reflect the insufficiency of the mitral valve which is frequently deformed in the persistent ostium primum defect. This is in contrast to the patient with a secundum type of atrial septal defect where the atrioventricular valves are not involved and the chambers of the left heart are always normal or small (fig. 3).

Electrocardiograms: The electrocardiogram is of diagnostic value in indicating the presence of an ostium primum type of atrial septal defect (fig. 4).* Left axis deviation was noted in the electrocardiograms of three of the five patients, in two of which there was horizontal electrical position and in the remaining one a vertical electrical position. The precordial leads indicated an incomplete right bundle branch block in four of the five patients, and in the remaining patient were clearly indicative of right ventricular hypertrophy. There was additional evidence suggesting right ventricular hypertrophy in the four patients having an incomplete right bundle branch block. The precordial leads revealed findings suggesting left ventricular hypertrophy in four of the five patients. The presence of left ventricular hypertrophy is difficult to determine from the electrocardiogram in the presence of hypertrophy and conduction disturbance of the right ventricle and these statements are influenced by comparison with the electrocardiograms of patients with known ostium secundum type defects.

The P waves were considered to be abnormal in the tracings of three of the five patients. There was considered to be evidence of right atrial enlargement in three patients (R. L., J. R., and M. O'C.) and suggestive evidence of left atrial enlargement in two of these patients. There was a normal sinus rhythm in all patients and the rates were within normal limits. There was evidence of first degree heart block and prolongation of the QRS interval in three patients according to the standards proposed by Ziegler.[8]

The analysis of the electrocardiograms in

* Table 1 in which the electrocardiographic findings are summarized is being omitted at the request of the Editor. This table will be furnished upon request.

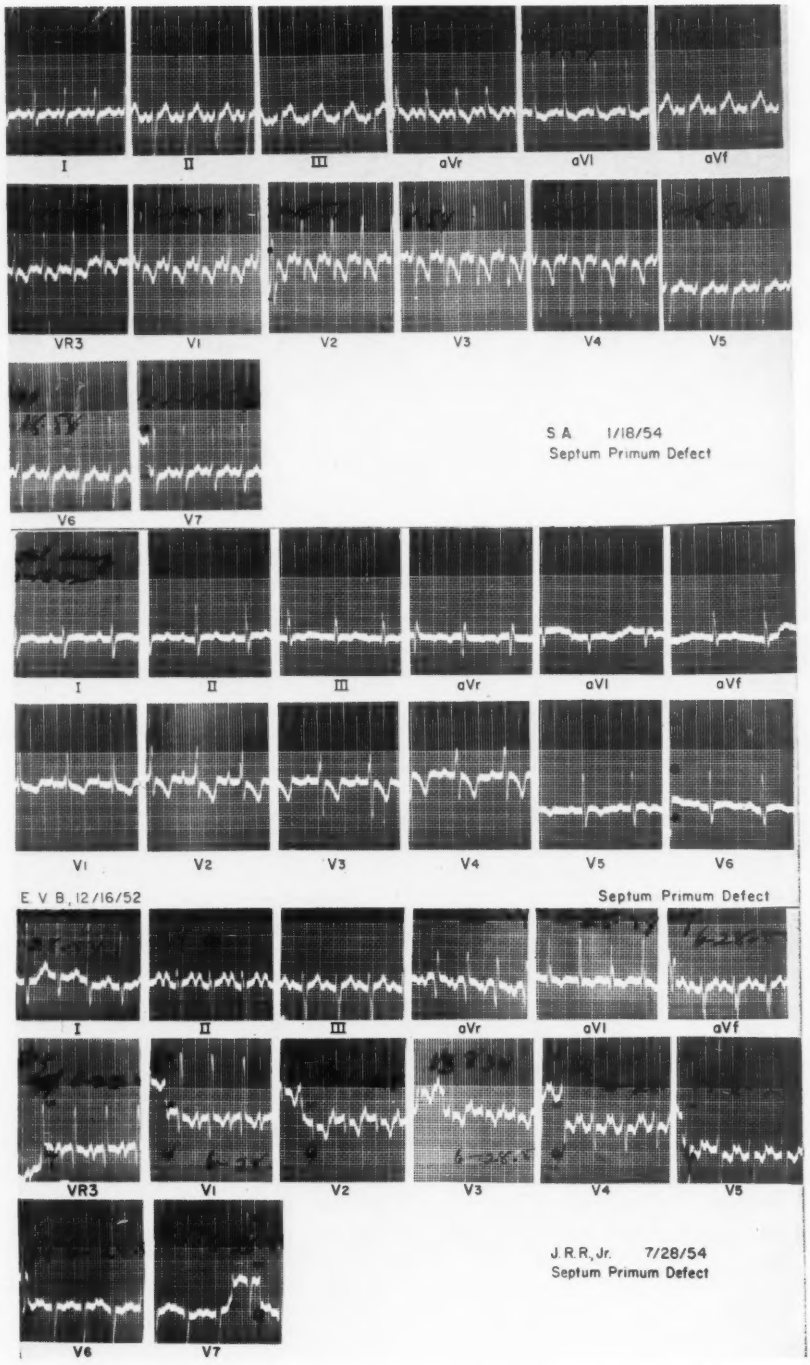
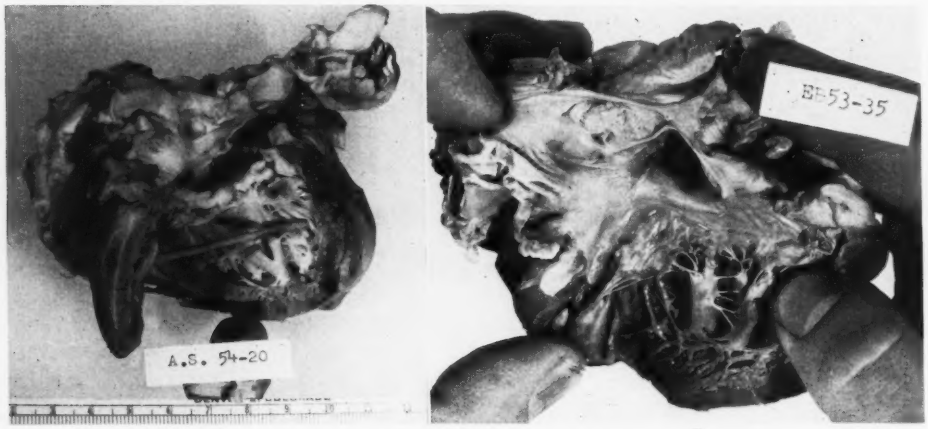


FIG. 4. Electrocardiograms of patients S. A. case 1, E. V. B., case 3, and J. R. R. case 4.



A *B*

FIG. 5. Views of Left Atrium; Mitral Valve and Left Ventricle in (*A*) patient A. S. case 1 and (*B*) patient E. B. case 3.

these patients is of particular value when compared with the tracings of 23 patients with established ostium secundum type of atrial septal defects.[7] There were no instances of left axis deviation nor horizontal electrical position of the heart in any patient in this latter group. There was no suggestion of left ventricular or left atrial enlargement in any of these 23 patients, and in none was there an R wave in V_6 of 21 mm. or greater. Thus, in patients with an ostium primum type defect the electrocardiogram differed strikingly from that seen in the ostium secundum defect, the sole exception being case 3 (E. B.); and it is of significance to note that this is the only one of the five patients in whom there was no involvement of the mitral valve (fig. 5*B*).

These variations from the typical electrocardiogram which is present in the patient with a known secundum type of defect are again considered to reflect the presence of mitral insufficiency and the resulting enlargement of the left ventricle.

Physiologic Data. Evaluation of the physiologic data revealed no features of distinct differential diagnostic value when compared with the data from patients with known ostium secundum defects (table 2). There was a suggestion that the volume of the left to right shunt was greater in patients with an ostium primum defect and that the pulmonary artery pressure was higher; however in the individual case these findings were of no definite diagnostic value.

The position of the catheter as it crosses over into the left atrium may be a helpful sign. A low position of this crossing would tend to suggest an ostium primum defect, further support of this contention being the easy entrance of the catheter into the left ventricle. The withdrawal of the catheter from a high pressure area containing highly oxygenated blood directly into a low pressure area with blood of a significantly lower oxygenation might also suggest the possibility of an ostium primum defect. Two patients had slight peripheral arterial unsaturation, an infrequent finding in patients with a secundum defect. There was no evidence of an additional left to right shunt at the ventricular level in any of these patients.

The features just discussed may be considered to be suggestive, but never diagnostic in the individual case. It is considered that the slight differences noted may be accounted for either on the basis of absence of the lowest portion of the atrial septum, the size of the defect, and the presence of mitral insufficiency.

Anatomic-Pathologic Data. The atrial septal defects were large, and the atrioventricular valves formed the floor of the defect in all patients. This was established at postmortem examination in three instances and at the

TABLE 2.—*Cardiac Catheterization Data*

Patient Age	Pressures (mm. Hg)						Blood Oxygen Contents Vols. % / Sat. %									Blood Flow L./min. = Flow / L./min/M² = Index		
	Pul. art.	Rt. vent.	Rt. atr.	Left atr.	Pul. cap.	Fem. art.	Sup. vena cava	Inf. vena cava	caval ave.	Rt. atr.	Rt. vent.	Pul. art.	Left. atr.	Pul. vein.	Fem. art.	A-V diff.	Pul. flow pul. index	Syst. flow syst. index	Shunt
Case 1							10.66	10.29	10.41	13.41	12.35		13.57		13.85	3.44	6.87	3.00	L to R
S. A.		42/8	8/3	21/12		100/75	77.1%	74.4%	75.7%	96.9%	89.3%		98.0%		100%		12.70	5.60	3.87
4 yrs.																			7.10
Case 2							10.46	12.42	11.77	13.02	12.75		14.09*	14.94	14.32	2.55	8.82	4.65	L to R
L. L.		28/4	8/5			69/52	63.4%	75.2	69.3%	78.9%	77.2%		85.4%	90.4%	86.7%		15.60	8.30	3.17
27 mo.																			7.30
Case 3							12.90	12.48	12.69	14.54	15.39	15.92	17.02	17.35	16.71	4.02	12.50	3.91	L to R
E. B.	15/7	21/3	5/0	7/1	6/4		71.4%	69.8%	70.6%	80.4%	85.1%	88.1%	94.1%	95.9%	92.4%		11.90	3.76	8.59
10 yrs.																			8.14
Case 4							9.7	11.1	10.6	11.4	11.65	11.8			12.7	2.1			
J. R	50/30	50/0	15/0		9		73.4%	84.1%	78.8%	85.9%	88.2%	89.2%			96.2%				
4 yrs.																			
Case 5							9.22	10.28	9.86	12.34	12.62	12.54	LA entered		13.17	3.31			
M. O'C.	48/20	36/3	5				62.2%	69.4%	66.5%	83.2%	85.0%	84.6%	but no sample		88.8%				
28 mo.																			

* Left ventricle also entered.

time of direct-vision, open-heart surgery in the remaining two patients. The area of the foramen ovale was noted in all instances and there was patency in one patient (case 3).

The atrioventricular valves were deformed in two of the three hearts available for postmortem examination (fig. 5 *A*). The mitral valve was more significantly involved in each instance.

The remaining patient (E. B.) of this group was found to have an ostium primum type defect at postmortem examination. However, he was the only patient that demonstrated no anatomical abnormalities of the atrioventricular valves. It is considered to be of interest and significance that in this patient there were no findings either on physical examination, in the electrocardiogram or upon fluoroscopy to indicate the possible presence of an ostium primum type defect. This patient, then, further supports the contention that abnormalties of the atrioventricular valves and, in particular, defects of the mitral valve give rise to the findings indicating the presence of the ostium primum type defect.

The location of the defect in the atrial septum is not considered to be of significance in the development of the distinctive pattern of the patient with this type of defect.

Although the anatomic details of the mitral valve are not known in the two patients still living, both mitral valves were functionally insufficient at the time of surgery. Prior to cessation of circulation the area of the defect and atrioventricular valves were palpated by the surgeon, Dr. Henry Swan. A regurgitant jet of blood was detected coming from the left ventricle back through the mitral valve into the right atrium as well as into the left atrium.

SUMMARY AND CONCLUSIONS

The five patients comprising this group all had large defects of the atrial septum. The defect was situated in the most caudal portion of the septum so that the atrioventricular valves in each instance formed the floor of the defect. These valves were abnormal in 4 of the 5 patients, the mitral valve in 4 and the tricuspid valve in 2. The mitral valve was considered to be insufficient in all four of these patients, and in two of the four it was definitely established at the time of surgery that this valve was incompetent. There was no evidence that the ventricular septum was defective in any of the five patients in this group.

These patients have thus been classified as having the persistent ostium primum type of atrial septal defect. It is realized that some will consider these patients to represent examples of a partial atrioventricularis communis type of defect. We do not deny that this is a logical

and acceptable designation. However, inasmuch as there was no clinical nor physiologic evidence in these five patients, nor anatomic evidence in the three patients postmortem that the ventricular septum was involved, we have chosen to designate this defect as the persistent ostium primum type of atrial septal defect.

Clinically, these patients tended to have larger hearts and to become symptomatic earlier than the patient with the ostium secundum type of defect. Physical examination revealed findings suggesting the presence of mitral insufficiency. The electrocardiogram frequently disclosed the presence of left axis deviation and evidence of left ventricular enlargement and, thus, differed from the rather characteristic tracing of the secundum type of defect. Fluoroscopy revealed no diagnostic features, although the heart tended to be larger and often there were findings suggestive of enlargement of the left ventricle. Cardiac catheterization yielded no diagnostic findings but the low position of the catheter as it crossed into the left atrium and at times the ease with which the catheter entered the left ventricle were suggestive findings. Therefore, these patients did not present a pathognomonic clinical picture, but there were certain features that differed from the findings in patients with a secundum type defect sufficiently to suggest the presence of the ostium primum type of atrial septal defect.

The location of the defect of the atrial septum is not considered to have a significant role in the production of the distinctive clinical picture. The anomalies of the mitral valve with the resulting mitral insufficiency are considered the basis of this differential diagnosis. These features are the presence of a murmur indicating mitral insufficiency, not present in the patient with a secundum type defect. The evidence of left ventricular enlargement frequently demonstrated by the electrocardiogram and fluoroscopy, and present at postmortem examination in two of the three hearts is the result of this mitral insufficiency.

Further evidence to support this conclusion is offered in the evaluation of case 3 (E. B.), who presented an entirely different clinical picture from the other four patients. The symptoms of this patient were minimal, the heart was only slightly enlarged (fig. 3) and there were no additional murmurs present other than those typical of a patient with a secundum type of atrial septal defect. The electrocardiogram was entirely different from those of the remaining four patients and it revealed only the changes indicative of a partial right bundle branch block. Thus, the clinical picture presented by this patient differed in no way from that of the patient with a secundum type of atrial septal defect. A clinical diagnosis of an ostium primum defect was not entertained in this patient and the diagnosis was made only after postmortem examination. The important fact is that this was the only patient that did not reveal congenital defects of the mitral or tricuspid valves.

This important exception further substantiates the belief that it is the involvement of the mitral valve with resulting mitral insufficiency that tends to differentiate the ostium primum type defect from the ostium secundum type of atrial septal defect.

Summario in Interlingua

Cinque patientes con un defecto atrio-septal del typo del ostio prime esseva studiate per methodos clinic e laboratorial. Le diagnose esseva verificate al tempore de chirurgia cardiac aperte e/o al tempore del autopsia. Le valvulas atrioventricular representava le fundo del defecto e esseva deformate in 4 del 5 patientes. Insufficientia mitral esseva presente como resultato de iste deformitate valvular in omne iste 4 casos. Le deformitate valvular resultava in un sufflante, altisonante murmure systolic, que esseva audibile supra le area apical e le area sternal sinistro-inferior, e in un deviation sinistrorse del axe e indications de hypertrophia sinistro-ventricular in le electrocardiogramma. Nos opina que le deformitate del valvula mitral es le base de iste deviationes ab le constatationes typic pro patientes con defectos atrio-septal del typo del ostio secunde e rende possibile le diagnose differential de persistente ostio prime sub le conditiones delineate in le presente reporto.

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The Significance of the Intensity and Time of Appearance of the Korotkoff Sounds in Auricular Fibrillation

By SIMON RODBARD, M.D. AND JACK MARGOLIS, M.D.

Aside from their value in the indirect determination of the blood pressure the sounds at the brachial artery provide other valuable clinical information. Their value in blood pressure determination in auricular fibrillation generally has been found to be limited. By using a simple technic involving the counting of the brachial-artery-sound deficit, a satisfactory, repeatable method of blood pressure estimation is achieved in such patients with marked pulse rate irregularities. Other information, including a rough estimation of left ventricular stroke output, pulse wave force and velocity, are also appraised by analysis of these bruits.

ASIDE from their common use for estimation of the blood pressure level,[1] the Korotkoff sounds also provide other useful clinical information. Thus, the intensity and duration of the sounds provide an appraisal of the volume of blood flowing through the artery under the cuff.[2] A calibrated contour of the upstroke of the pulse wave, as well as an estimate of the celerity of its transmission rate, can also be established.[3]

The present study provides evidence that the time of onset of the sounds during the cardiac cycle is related to the diastolic filling time. In auricular fibrillation the determination of the incidence of the sounds at various cuff pressure levels permits a satisfactory measure of the blood pressure level despite irregularities of the pulse.

METHODS

The sounds at the brachial artery were recorded simultaneously with lead II of the electrocardiogram in seven patients with auricular fibrillation. The pressure in the sphygmomanometer cuff was first raised to levels higher than systolic in order to occlude blood flow to the extremity. The patient was then instructed to open and close his fist 30 times in order to induce a reactive hyperemia of the limb. The pressure in the cuff was then permitted to fall at a constant rate. In other experiments it was lowered by increments of 10 mm. Hg, and 10 to 20 cardiac cycles were recorded at each of these pressure levels.

Each cycle length was measured as the R-R interval. The time of arrival of the sound in each cycle was measured and this value was compared with the duration of the previous cycle. The logarithmic intensity and duration of the sound were determined directly from the photographic record as millimeters of swing of the galvanometer.

RESULTS

(1) *Effect of Cuff Pressure on the Ratio of the Incidence of Korotkoff Sounds to that of the R Waves.* The ratio of the incidence of the Korotkoff sounds to the number of electrocardiographic cycles provided a satisfactory means for a blood pressure determination (fig. 1). At sufficiently high cuff pressures, no sound was heard or recorded. As the cuff pressure was lowered by increments from these high levels in a given patient, a point was reached at which occasional sounds could be heard and then the ratio of Korotkoff sounds (K) to electrocardiographic QRS complexes (R) increased rapidly. Within a range of about 10 mm. Hg, the K/R ratio increased from zero to about 50 per cent. A further drop of cuff pressure of 10 or 20 mm. Hg increased the ratio usually to about 90 per cent or more; i.e., 9 of each 10 electrocardiographic complexes were followed by Korotkoff sounds.

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Dr. Margolis is a trainee of the National Heart Institute.

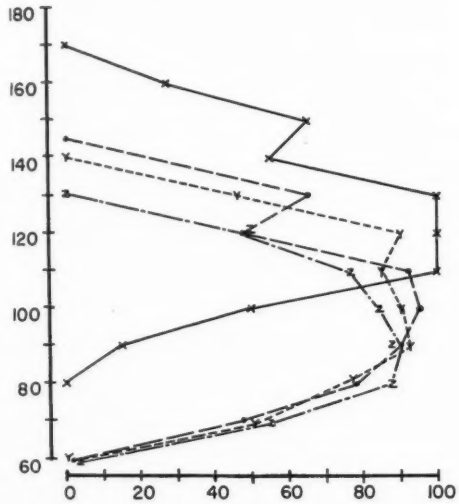

FIG. 1. The ratio of the number of sounds recorded at the brachial artery to the number of electrocardiographic cycles, at various levels of cuff pressure in four patients. Cuff pressure is given in the vertical axis; ratio of sounds to electrocardiographic cycles is given in the horizontal axis. The increasing incidence of sounds is depicted as cuff pressure falls from above systolic to mean pressures. At a point below mean arterial pressures, the incidence falls again, reaching zero at 80 mm. Hg cuff pressure in one subject depicted and 60 mm. Hg in the other three shown. Discussed in text.

As the cuff pressure was lowered further, the ratio of sounds remained at about 90 per cent, until a point was reached at which the K/R ratio began to fall. In the course of a 10 mm. Hg drop the ratio fell to about 50 per cent. With a further drop of 10 or 20 mm. Hg, all sounds disappeared. These were consistent findings in all seven patients studied.

These data show, as is well appreciated,[4] that significant fluctuations may occur in both systolic and diastolic blood pressure from beat to beat in patients with auricular fibrillation. However, despite these variations a definite and repeatable blood pressure level could be established. The present findings that the ratio of occurrence of Korotkoff sounds to electrocardiographic cycles approaches 50 per cent in a well demarcated cuff pressure zone shows the possibility of obtaining a satisfactory mean systolic and mean diastolic blood pressure level in patients with marked cardiac arrhythmias.

(2) *Relation of Preceding Cycle Length to the Incidence of the Korotkoff Sounds.* The likelihood of occurrence of the Korotkoff sounds obtained at each given cuff pressure level correlated well with the duration of the preceding cycle. Thus, when the preceding length was less than 0.40 second, no Korotkoff sound was heard in the immediately succeeding beat. For preceding cycle lengths ranging between 0.42 and 0.48 second the sounds were heard irregularly. It is likely, though our data are insufficient to establish this, that the incidence of occurrence of the sounds increases in a regular fashion with the length of the preceding cycle length in this range. When the preceding cycle lengths were 0.50 or more, a sound was always heard.

(3) *Relationship of Amplitude of Sound to Previous Cycle Length.* The amplitude of the sounds could be correlated grossly with the duration of the previous cycle. This is illustrated by the data presented in figure 2, obtained in a single continuous run on a patient with fixed setting at level 3 of the gain control of the phonocardiographic machine, and with

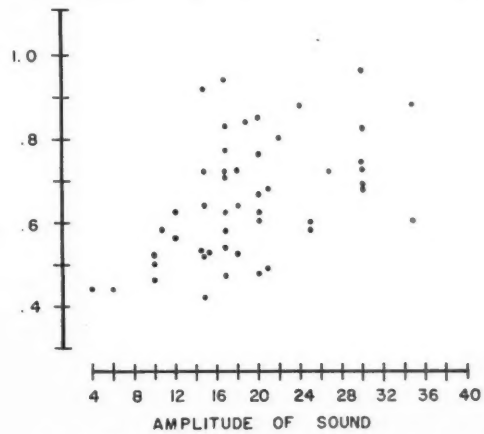

FIG. 2. Relation between previous cycle length and amplitude of the sound recorded at the brachial artery. All points given were obtained in a continuous run with cuff pressure maintained at 100 mm. Hg. The duration of the previous cycle is given as the R-R distance in the vertical axis. The amplitude of the recorded sound is given on the horizontal axis. Each point represents a single determination.

the cuff pressure held constant at 100 mm. Hg. As noted above, cycles of less that 0.4 second were not followed by an arterial sound. When the previous cycle ranged about 0.5 to 0.6 second, the amplitude for a given cuff pressure averaged 12 to 14 mm. With longer cycle lengths of approximately 0.8 second, the amplitude averaged 20 mm.

(4) *Relationship between Durations of Sound and of the Previous Cycle.* A general correlation was also shown between the durations of each cycle and of the succeeding sound (fig. 3). This relationship was most apparent at cuff compressions equal to about mean blood pressure values. At cuff pressure values approaching either the systolic or diastolic pressure levels, difficulties in the analysis were present, due in part to the fact that some of the pulses did not produce sounds.

(5) *The Time of Onset of Korotkoff Sounds.* In subjects with a regular cardiac rhythm, the time of onset of the brachial artery sound remains constant (±0.01 second) from beat to beat.[5] However, in patients with cardiac irregularities, as in auricular fibrillation, the time of onset of the sound can be shown to be related inversely to the duration of the previous cycle (fig. 4). For example, at a cuff pressure of 100 mm. Hg, the onset of the Korotkoff

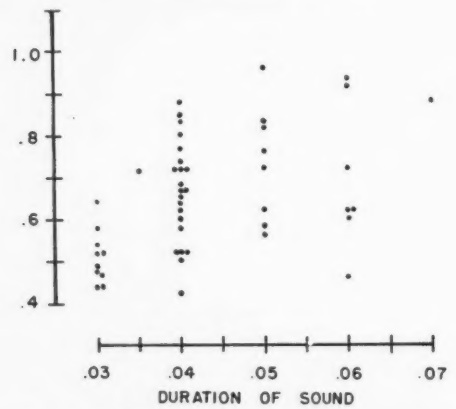

FIG. 3. Relation between the duration of the previous cycle length and the duration of the sound registered at the brachial artery. Vertical axis gives the duration of the cycle previous to the occurrence of the sound. Duration of the sound is given in seconds on the horizontal axis. These data are from the same undisturbed run described in figure 2.

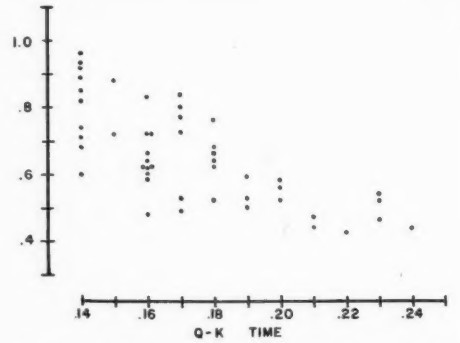

FIG. 4. The relation between the duration of the previous cycle to the time of onset of the brachial artery sound. The points given are for the same undisturbed run described in figure 2. Vertical axis gives the previous cycle length in seconds. Horizontal axis gives the time in seconds from onset of the QRS complex of the electrocardiogram until the onset of the sound at the brachial artery.

sounds occurred at approximately 0.20 second when the preceding cycle was short (0.5 second); with longer preceding cycles this was reduced to as little as 0.13 second for long cycle lengths approaching 1 second. As noted above, and demonstrated in figure 4, there was an absence of brachial artery sound when the previous cycle lengths were less than 0.40 second.

DISCUSSION

In auricular fibrillation, the incidence of sound production at the systolic and diastolic levels may be very irregular. This effect is enhanced by a tendency to an "auscultatory gap" in such patients, as suggested by the fall in incidence of sounds at about 30 mm. below the highest recorded systolic values (fig. 1). As a result, variations of 30 or 40 mm. Hg in the indirect estimation of the systolic blood pressure level, and somewhat smaller deviations of the diastolic, may be reported for a given patient by successive observers.

The present results suggest that a satisfactory measure of the mean systolic and diastolic pressures may be established by determining the ratio of the Korotkoff sounds to cardiac cycles at each of several cuff pressure levels. As the cuff pressure falls below the systolic pressure the ratio of the brachial artery sounds per minute increases over the course of about

2) mm. Hg until it reaches a maximum rate. The number of cardiac cycles per minute may be obtained at the precordium as is done for determination of the pulse deficit, or by electrocardiographic monitoring. A *mean systolic* blood pressure level may be considered as that cuff pressure at which half of the apical beats are followed by brachial artery sounds, i.e., a deficit of 50 per cent.

As the cuff pressure falls further into the range of the diastolic pressure the incidence of the sounds is reduced progressively. When the incidence is reduced to about half that obtained at mean blood pressure, this value, obtained at a consistent level in each patient, may be considered to be the mean diastolic pressure.

The fact that no brachial artery sound was heard when the preceding cycle was less than 0.40 second is consistent with data that a short cycle may be inadequate to produce a pulse wave in the arterial system, probably as a result of inadequate filling of the ventricle, and the consequent weak or absent ejection phase. With cycle lengths longer than 0.5 second, the succeeding beats consistently produced a brachial sound, indicating that this duration in the patients studied was sufficient for pulse wave production.

In previous studies it has been demonstrated that the onset of the Korotkoff sounds signals the arrival of a pressure pulse equal to the compressing pressure in the sphygmomanometer cuff. The present studies suggest that the duration of the previous cycle can affect the time of arrival of the pulse wave. Thus, the greater the duration of the previous cycle, the shorter is the Q-K time of the succeeding beat. Such an effect might be due to a change in the rate of transmission of the pulse wave because of variations in the diastolic filling time and perhaps in stroke volume of the succeeding beat. This belief is supported by other evidence that the celerity of the transmission of the arterial pulse wave is related to the stroke volume.[5] If this is proved to be the case, the time of arrival of the brachial artery sounds might provide an index of the relative stroke volume for successive beats.

The intensities of the brachial artery sounds probably are also related to the rate of rise of pressures in the aorta and in the brachial artery central to the cuff. The more powerful pressure pulse generated following longer cycle lengths thereby are seen as establishing the conditions for a louder burst of noise at the onset of the Korotkoff sound.

The relationship between the duration of the previous cycle and the intensities and durations of the brachial sounds also is consistent with the interpretation that an enhanced stroke output following a prolonged filling period is associated with a more forceful pulse wave causing a more adequate flow through the arteries under the cuff.

The foregoing studies illustrate that significant clinical information concerning some of the characteristics of the arterial pulse wave, the blood pressure and the blood flow through extremities may be obtained indirectly and with facility by utilizing the intermediate Korotkoff sounds.

Summary

Simultaneous recording of the sounds at the brachial artery and of the electrocardiogram in seven patients with auricular fibrillation provided a basis for satisfactory estimation of the mean systolic and mean diastolic blood pressure levels. To obtain these values, the rate of occurrence of brachial sounds at a mean arterial pressure to apical beats is first determined. Higher or lower cuff pressures at which this rate is reduced to about 50 per cent are then used to determine the mean systolic and diastolic pressures respectively.

The time of the sounds and their intensities and durations are related to the duration of the preceding cardiac cycle and to a factor dependent on the blood pressure and the compression produced by the cuff.

For very short preceding cycles, no Korotkoff sound is heard or recorded. With longer preceding cycles, sounds are heard. The time from the Q wave of the electrocardiogram to the onset of the sound is shortened as the preceding cycle is more prolonged. This suggests that the transmission time of the pressure pulse wave in the arterial tree may be related to the stroke output. The intensity and dura-

tion of the sound, at least at mean arterial pressure levels, is also associated with the duration of the previous cycle, and presumably with the stroke output.

Summario in Interlingua

Le simultanee registration del sonos al arteria brachial e del electrocardiogrammas in septe patientes con fibrillation auricular esseva usate como base pro estimar le median nivellos del systolic e diastolic pression sanguinee. Pro obtener iste valores nos primo determina le frequentia del sonos brachial a un median pression arterial. Postea le plus alte o plus basse pressiones de bracial pneumatic al quales ille frequentia es reducite a 50 pro cento es usate pro determinar le median pressiones systolic e diastolic, respectivemente.

Le momento del sonos e lor intensitates e durationes es ponite in relation con le duration del precedente cyclo cardiac e con un factor que depende del pression sanguinee e del compression producite per le bracial pneumatic.

In le caso de brevissime cyclos precedente, nulle sono de Korotkoff es registrate o audite. In le caso de plus longe cyclos precedente, sonos de Korotkoff deveni audibile. Le intervallo de tempore ab le unda Q del electrocardiogramma usque al declaration del sono deveni plus breve in tanto que le cyclo precedente deveni plus longe. Isto pare indicar que le tempore de transmission del unda pulsatil de pression in le arbore arterial es possibilemente relationate a rendimento cardiac. Le intensitate e le duration del sono—al minus a nivellos median del pression arterial—es etiam associate con le duration del cyclo precedente e probabilemente con le rendimento cardiac.

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Fluorescent Patterns of Intracutaneous Wheals in Normal and Edematous Extremities

By Ray W. Gifford, Jr., M.D., John H. Windesheim, M.D., J. Earle Estes, Jr., M.D., and Grace M. Roth, Ph.D.

Intradermal injection of a fluorescent dye (riboflavin) and ultraviolet light were used to demonstrate cutaneous lymphatic capillaries. The extremities of a control group and the nonedematous extremities of patients with arteriosclerosis obliterans were studied together with edematous extremities of patients with lymphedema, acute thrombophlebitis, chronic venous insufficiency and various other conditions.

The lymphatic capillaries showed up more extensively after a higher percentage of injections into edematous extremities of patients with lymphedema than after injections into the other extremities. On the other edematous extremities except in the cases of nephrotic syndrome and on the normal extremities, either no lymph capillaries or only a few were visible after most of the injections.

DURING the course of a previous investigation[1] it became apparent that after intradermal injections of a fluorescent substance (riboflavin), a network of capillaries could be demonstrated with greater ease and frequency in the skin of extremities affected by lymphedema than in normal ones.

Subsequently, we have extended our studies to include more than 200 patients and normal subjects. This report is a summary of our findings.

Methods and Materials

Intradermal wheals were made by injecting 0.1 cc. of a solution containing 2.5 mg. of the sodium salt of riboflavin (Flavaxin*) per cubic centimeter. Tuberculin syringes and well-sharpened 27-gage, one-half inch long hypodermic needles were used. The injections were made with the subjects in the supine position in a darkened room so that the resultant fluorescent wheals and patterns could be observed immediately under a portable ultraviolet lamp.†

These studies were confined to the lower extremities in every case except for one woman in whom a lymphedematous upper extremity was injected.

In most cases the intracutaneous injections were made on the medial aspect of the leg about 3 or 4 cm. superior to the internal malleolus. When pigmentation or ulceration precluded use of this site, injections were made more superiorly. When edema was confined to the dorsum of the foot, injections were made in that region also. Usually more than one injection was made in each extremity studied.

When the intradermal wheals are being made, caution must be exercised lest the injection be too deep in which case the typical patterns will not appear. If any of the solution leaks onto the surface of the skin, surface fluorescence will obscure the underlying pattern.

Selection of Normal Subjects and Patients

For control, injections were made into the skin of the lower extremities of 71 persons who had no history or objective evidence of peripheral edema or any circulatory disorder affecting the lower extremities. Many of these persons were physicians, nurses, secretaries and laboratory technicians. Others were patients, most of whom were hospitalized for treatment of essential hypertension and none of whom had any evidence of disease in the lower extremities. All consented to the procedure.

An attempt was made to study as many patients with edema of the lower extremities as possible provided that the cause of the edema was not complex and was well established. Many of the patients did not have edema at the time of the injections. The condition of the patients and the number in each group will be considered when the observations are reported.

Appearance and Classification of Fluorescent Patterns

A brilliant yellow fluorescent wheal immediately appears when the solution of ribo-

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* Furnished for this study by Winthrop-Stearns, Inc., New York.

† A General Electric CH-4 spot projector with a 100-watt lamp was used for these studies.

flavin is properly injected into the skin and the region is viewed under ultraviolet light. When the volume of the injection is 0.1 cc., the diameter of the wheal is approximately 1.0 cm. and is remarkably constant except in some edematous extremities where it may be smaller. In addition to the wheal which inevitably appears after all injections, in many extremities, an intertwining reticular pattern may be observed at the periphery of the wheal. This fluorescent reticular network, if present, may form a partial or complete halo around the circumference of the central wheal and may vary from a few millimeters to as much as 10 cm. in width. In general, the larger the reticular pattern, the smaller the central wheal. In some instances, fluorescent reticulation may be seen at some distance from the central wheal and separated completely from it. We have called such discrete and separate areas "islands" after McMaster's terminology.[2]

For reasons to be developed subsequently, we have decided that the reticular network represents cutaneous lymphatic capillaries that are filled with the fluorescent solution. If the injections are made under ultraviolet light, the wheal and its surrounding reticular pattern appear simultaneously and promptly. The wheal persists for several hours, but the fine reticulated network surrounding it rapidly loses its identity and soon becomes a diffuse area showing only dim fluorescence. For this reason it is imperative to observe the fluorescent pattern immediately after each injection. Subcutaneous "streamers," as described by McMaster,[2] were observed with such irregularity that they were not considered in evaluating the patterns. Furthermore no attempt was made to time the disappearance of the fluorescent areas since this was the subject of a previous investigation.[1]

To facilitate the reporting of results the patterns observed were arbitrarily classified into five types as follows:

Type 0 is characterized by a fluorescent wheal with no surrounding reticular network (fig. 1).

Type 1 is characterized by a fluorescent wheal with complete reticular halo not exceeding 1 cm. in its greatest width or an incomplete reticular halo not exceeding 2 cm. in width (fig. 2).

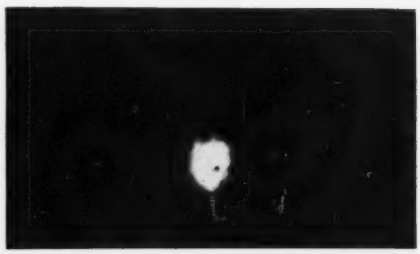

FIG. 1. Pattern of type 0. Solid yellow, fluorescent wheal with no surrounding reticular network.

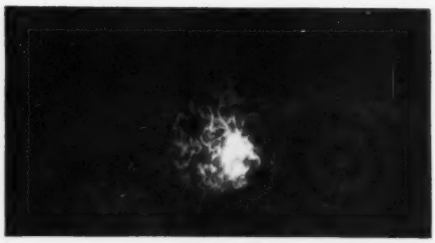

FIG. 2. Pattern of type 1. Central wheal partially surrounded by incomplete halo of reticular network not exceeding 2.0 cm. in greatest width.

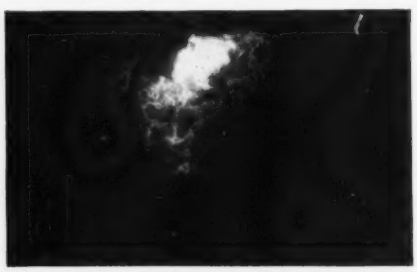

FIG. 3. Pattern of type 2. Central wheal partially surrounded by incomplete halo of reticular network which is 3 cm. in greatest width.

Type 2 is characterized by a fluorescent wheal with complete reticular halo greater than 1 cm. but not exceeding 2 cm. in its greatest width or an incomplete reticular halo from 2 to 4 cm. in greatest width (fig. 3).

Type 3 is characterized by a fluorescent wheal with complete reticular halo greater than 2 cm. but not exceeding 4 cm. in its greatest width or an incomplete reticular halo greater than 4 cm. in greatest width (fig. 4). f

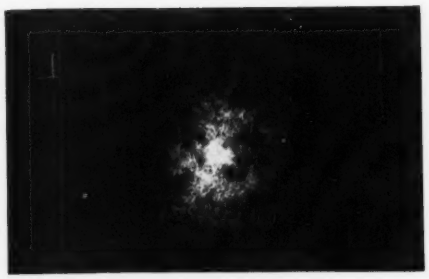

FIG. 4. Pattern of type 3. Central wheal completely surrounded by halo of reticular network which is 3 cm. in greatest width.

"islands" were present, the pattern was considered to be at least type 3 regardless of whether the other criteria were present.

Type 4 is characterized by a fluorescent wheal with complete reticular halo exceeding 4 cm. in its greatest width with or without "islands."

In this and a previous investigation[1] well over 1,500 intracutaneous injections of solutions of riboflavin have been made with no untoward results. Pain resulting from the injections is no greater than that experienced after intracutaneous injection of a similar volume of any nonirritating solution.

PATTERNS OF "NORMAL" SUBJECTS

Of the 71 so-called normal subjects whose legs were injected with riboflavin as a control, 41 were men. The ages of all varied from 19 to 66 years; the mean age was 40 years. The frequency with which the various patterns were observed in normal legs is given in table 1. None of the 268 injections into normal legs resulted in a pattern of type 4 and only four injections resulted in patterns of type 3. Two women and one man in each of whom one pattern of type 3 was observed were suffering from essential hypertension but none had ever had peripheral edema. The fourth pattern of type 3 was observed in the leg of a female physician, aged 26 years. Each of these four subjects received three additional injections which resulted in patterns of types 0 and 1. "Islands" were observed in three of the four patterns in this group which were classified as type 3.

PATTERNS OBSERVED IN PATIENTS WITH ARTERIOSCLEROSIS OBLITERANS

Twelve patients suffering from arteriosclerosis obliterans of the lower extremities were studied. All had ample evidence of severe ischemia but none had ever noted peripheral edema. Ten were men. The ages of all varied from 38 to 83 years and the mean age was 62 years. The frequency with which the various fluorescent patterns were observed in this group is given in table 1. None of the 34 injections resulted in a pattern of type 4 and only one, which was made into an 83-year-old woman, resulted in a pattern of type 3. Three additional injections into the legs of this woman resulted in patterns of types 1 and 2. No "islands" were noted.

A 62 year old man who had arteriosclerosis obliterans was not included in this group of 12 patients because he also had had severe edema of undetermined etiology in both legs for nine months prior to the injection. Numerous injections into this man's legs resulted repeatedly in patterns of types 2, 3 and 4 without islands.

Because the patterns observed in the ap-

TABLE 1.—*Results in Extremities with No Edema*

Condition	Patients	Legs	Injections	Per Cent of Injections					
				Type 0	Type 1	Type 2	Type 3	Type 4	Islands*
Normal	71	142	268	48.1	48.9	1.5	1.5	0	1.1
Arteriosclerosis obliterans	12	24	34	23.5	64.7	8.8	3.0	0	0
Total	83	166	302	45.4	50.7	2.3	1.6	0	1.0

* Instances in which islands occur are also included with results listed as type 3 or 4 in this and the other ables.

parently normal extremities and in extremities with arteriosclerosis obliterans without edema were so nearly identical, the sum of the two were used (table 1) to represent results in extremities free of edema for comparison with results obtained in edematous extremities.

Patterns Observed in Lymphedema

Lymphedema Praecox. Twenty-four patients had lymphedema praecox. Twenty were females. The ages of all patients varied from 18 to 81 years and the mean age was 39 years. Lymphedema had been present for three weeks in one patient and for 74 years in another. The average duration of edema was 14 years. Only six of the extremities were not edematous or enlarged at the time of the injections. The frequency with which the various patterns were observed is shown in table 2.

Injections failed to produce at least one pattern of type 3 or 4 in only five legs of four patients. Of these five legs, two were injected only once each and one had been edematous for only five months. The fourth was that of a man, 81 years old, who had had lymphedema of the left leg for 74 years. Despite a Kondoleon operation 30 years previously at which time the leg was estimated to weigh 110 pounds, the limb was massive at the time of the injections. The skin felt and looked like the bark of a tree. Repeated injections into this leg resulted only in patterns of types 0 and 1. The fifth leg which failed to show patterns of types 3 or 4 had been edematous for 23 years and was so cumbersome from chronic enlargement that a modified Homan's operation was undertaken.

Patterns of types 3 and 4 were seen as frequently in extremities with minimal or no edema at the time of injections as in extremities that were grossly edematous. In four extremities injections were repeated after the amount of edema had been reduced by a period of rest in bed with elevation of the legs. In none did the patterns produced by the second injections change appreciably as compared with the first.

In general the duration of edema had no effect on the patterns observed. Patterns of types 3 and 4 were seen as frequently in extremities that had been edematous for less than six months as in those that had been edematous for 10 to 20 years. When edema had been present for more than 20 years, however, patterns of types 3 and 4 tended to be less frequent.

Islands were noted after almost 50 per cent of the injections.

Obstructive Lymphedema. Twelve patients with lymphedema secondary to lymphatic obstruction were studied. The obstruction was caused by metastatic carcinoma in 10 patients and by Hodgkin's disease in one, and it followed radical mastectomy in one. Seven of the patients were females. The ages of all varied from 38 to 69 years and the mean age was 53 years. The duration of edema at the time of the injections varied from 1 week to 14 years with a mean of 18 months. Fourteen of the 17 involved extremities had been edematous for less than nine months, however. All but two extremities showed pitting edema at the time of the injections and in eight it was graded 3 or 4 (on a grading basis of 0 to 4). The fre-

Table 2.—*Results in Extremities with Lymphedema*

Condition	Patients	Legs	Injections	Per Cent of Injections					
				Type 0	Type 1	Type 2	Type 3	Type 4	Islands
Lymphedema praecox	24	36	98	12.2	10.2	13.3	42.9	21.4	44.9
Obstructive lymphedema	12	17*	42	16.7	14.3	23.8	35.7	9.5	23.8
Miscellaneous types of lymphedema	6	9	17	0	11.8	5.9	70.5	11.8	47.0
Total	42	62	157	12.1	11.5	15.3	43.9	17.2	39.5

* Includes one upper extremity.

quency with which the various patterns were observed in this group are shown in table 2. Injections into 5 extremities of 4 patients failed to show at least one pattern of type 3 or 4. All of these five extremities had been edematous for less than six months. Patterns of types 3 and 4 were seen oftener in extremities which had been edematous for six months or longer. There was also a direct, though less striking, correlation between the degree of edema at the time the injections were made and the frequency of patterns of types 3 and 4.

Islands were observed much less frequently in obstructive lymphedema than in lymphedema praecox.

Miscellaneous Types of Lymphedema. Two patients with primary inflammatory lymphedema, three with secondary inflammatory lymphedema and one with lymphedema owing to prolonged dependency of the legs from arthritic contractures of the knees are included in this group. Three were females. The ages of the six patients varied from 20 to 69 years with a mean of 41 years. The duration of edema at the time the injections were made ranged from 7 months to 10 years with a mean of 4 years. All extremities were edematous when the injections were made, although only two were markedly so (grade 4). The frequency with which various patterns were observed is shown in table 2. Only one extremity failed to show at least one pattern of type 3 or 4, and this extremity was injected only once. A high incidence of islands was noted in this group.

Patterns Observed in Extremities with Edema Other than Lymphedema

Acute Thrombophlebitis. Seventeen patients with acute thrombophlebitis of one or both lower extremities were included in this study. Ten were males. The ages of all ranged from 16 to 69 years with a mean of 49 years. The diagnosis was acute iliofemoral thrombophlebitis in 14 extremities and thrombophlebitis deep in the calf in four. The duration of symptoms at the time that the injections were made varied from one day to three weeks with a mean of 10 days. Five extremities were not edematous at the time of the injections and in three the pitting edema was graded as 3 or 4. The frequency with which the various patterns were observed is shown in table 3. No injections resulted in patterns of type 3 or 4.

Chronic Venous Insufficiency. Twenty-seven patients with chronic venous insufficiency of one or both lower extremities were included. Nineteen were males. The ages of all ranged from 26 to 78 years with a mean of 48 years. The duration of symptoms of venous insufficiency at the time the injections were made ranged from 1 month to 30 years; the mean was 11 years. Many of the extremities exhibited pigmentation characteristic of chronic venous insufficiency and a few showed stasis ulcers. Previous treatment had rendered 28 extremities free of pitting edema at the time of the injections. In only two extremities was the pitting edema graded 3 or 4. The frequency with which the various patterns were observed is shown in table 3. No pattern of type 4 was observed. A total of 11 injections into 10 extremities of nine patients resulted in patterns of type 3. Islands were observed after nine injections. All 11 of the patterns of type 3 were observed in extremities which had no edema or only slight edema (grade 1) when the injections were made. Nine of the 11 patterns of type 3 were observed in extremities in which the symptoms of chronic venous insufficiency had been present for 10 or more years.

Lipedema. Ten patients with lipedema[3] were included. All were women and their ages ranged from 35 to 59 years with a mean of 50 years. The duration of symptoms at the time the injections were made varied from 1 to 50 years with a mean of 23 years. Although all patients had the thick ankles and fat legs characteristic of this condition, only two had pitting edema when the injections were made. The frequency with which the various patterns were observed is shown in table 3. A total of seven patterns of types 3 and 4 were observed in five legs of three patients. Islands were noted after three injections. Two of the three patients whose legs showed patterns of types 3 and 4 had had lipedema for 25 years. The third had had symptoms for 13 years. In two of the five legs in which patterns of types 3 and 4 were seen pitting edema was present when the injections were made.

TABLE 3.—*Results in Extremities with Other Types of Edema*

Condition	Patients	Legs	Injections	Per Cent of Injections					
				Type 0	Type 1	Type 2	Type 3	Type 4	Islands
Acute thrombophlebitis	17	18	27	25.9	70.4	3.7	0	0	0
Chronic venous insufficiency	27	43	82	23.2	51.2	12.2	13.4	0	11.0
Lipedema	10	20	42	45.2	33.3	4.8	9.6	7.1	7.1
Simple orthostatic edema	5	10	20	50.0	40.0	0	10.0	0	10.0
Congestive heart failure	19	37*	75	30.7	57.3	9.3	2.7	0	1.3
Nephrotic syndrome	6	12	24	12.5	45.8	16.7	20.8	4.2	16.7

* One patient had unilateral lymphedema also; the leg so affected was not included.

Simple Orthostatic Edema. The lower extremities of five patients with simple orthostatic edema were injected. This syndrome is characterized by mild to moderate pitting edema of the ankles related to orthostatism and often aggravated by warm weather, menses and the menopause. No objective evidence for other causes of edema is found. Two of the patients included in this group would actually have been classed as normal except for a history of minimal and extremely intermittent swelling of the ankles noted at the end of a day. The other three patients had more persistent and troublesome edema of the ankles. All the patients were women from 25 to 58 years of age with a mean age of 46 years. Symptoms had been present from 7 months to 20 years with a mean of 8 years. Only one patient had demonstrable pitting edema of the legs at the time the injections were made. The frequency with which various patterns were observed is shown in table 3. No pattern of type 4 was observed and only two injections resulted in patterns of type 3 (both with islands). These two patterns were noted in the legs of a 24-year-old woman who had experienced intermittent ankle edema for four years but no edema was present at the time of the injections.

Congestive Heart Failure. Nineteen patients with congestive heart failure severe enough to cause ankle edema were included. Fourteen were males. The ages of all patients ranged from 36 to 81 years and the mean was 55 years. Edema had been present continuously or intermittently for one day to five years. The mean duration was 10 months. Prior treatment had rendered the extremities of four patients free of edema before the injections were made, but 19 extremities had pitting edema of grade 3 or 4. The frequency with which various patterns were observed in this group is given in table 3. Only two injections resulted in patterns of type 3, and no patterns of type 4 were observed. One of the patterns of type 3 was seen in the leg of a 62-year-old woman who had had edema of the ankles secondary to congestive heart failure (hypertensive) for 13 months. The pitting edema was classified as grade 1 when the injection was made. The other pattern of type 3 was observed in the leg of a man, aged 71 years, who had noted edema of the ankles for only one day prior to the injection. The pitting edema was classified as grade 2 when the injection was made.

Nephrotic Syndrome. The lower extremities of six patients with nephrosis were injected. Four of these patients were males. The ages of the six varied from 30 to 63 years with a mean of 44 years. The duration of edema at the time the injections were made varied from 10 weeks to 2½ years with a mean of 14 months. All extremities were severely edematous (grade 3 or 4) when the injections were made. The frequency with which the various patterns were observed in these patients is shown in table 3. One pattern of type 4 and five of type 3 were encountered after injections into six extremities of four patients. Islands were seen after four injections. Three of the five patterns of type 3 were seen in extremities that had been edematous for less than 6 months. Patterns of type 1 were observed in the legs of the patient who had had edema for two and one-half years.

Miscellaneous Conditions. Two patients had

pitting edema of the lower extremities owing to hypoproteinemia from causes other than nephrosis and cirrhosis of the liver. The duration of edema was less than three months in both cases and all patterns observed were of types 0 and 1.

One patient had had edema of the ankles intermittently for six months owing to therapy with hydralazine (Apresoline). No edema was present at the time of the injections, and all patterns observed were of type 1.

Two patients who had massive edema of the lower extremities secondary to decompensated hepatic cirrhosis were included. Patterns of type 3 were noted in three of the four extremities and islands were noted in one. The edema had been present for three months in one case and 11 months in the other.

Patterns Observed in Apparently Normal Companion Extremities of Patients with Unilateral Edema

Thirty-nine patients had unilateral edema of the lower extremities and their apparently normal extremities were injected as well as the edematous ones. In only one of these apparently normal extremities was a pattern of type 4 noted. The disease in the opposite leg of this patient was lymphedema praecox. One pattern of type 3 developed in the apparently normal leg of a patient with acute iliofemoral thrombophlebitis in the opposite leg. Patterns of type 2 were noted in the apparently normal legs of two patients who had unilateral lymphedema praecox. In the remaining 35 patients with unilateral edema, all patterns observed in the apparently normal extremities were of types 0 and 1.

Comment

We do not claim to be measuring lymph flow by the technic described. It is our assumption, however, that the reticular network surrounding the central wheal represents the ramifications of cutaneous lymphatic capillaries which become filled with the fluorescent solution during the injection. Specimens of lymphedematous skin and subcutaneous tissue obtained at operation were injected repeatedly and a typical reticular pattern was obtained; unfortunately however, the riboflavin solution was lost in the process of preparing the tissue for sections. As a result microscopic confirmation that the solution of riboflavin is actually in cutaneous lymphatic capillaries is lacking. Hudack and McMaster[4], however, have injected India ink and gelatin into the skin and have found on examining such specimens microscopically that the superficial plexus of lymph vessels and the deeper-draining trunks are filled.

Hudack and McMaster[4] also emphasized that the lymphatic capillaries filled immediately after the injection. Our observations confirm this. These investigators were able to demonstrate a cutaneous network of lymphatic capillaries after nearly every intradermal injection of nonfluorescent dyes, and they consequently stated that, because of the extensive intertwining network of lymphatic capillaries in human skin, every intracutaneous injection was to some extent an intralymphatic injection.

Under the conditions of our investigation, however, we found that cutaneous lymphatic capillaries were filled poorly or not at all in normal as well as in many edematous extremities. In sharp contrast, we found that extensive capillary networks were demonstrated with relative ease in extremities affected by lymphedema. This observation also has been made by Kinmonth and Taylor[5] while using a nonfluorescent dye, patent blue V.

This naturally leads to the speculation that dilated capillaries of an incompetent lymphatic system are an easy target for the needle and become filled with the solution of riboflavin. Normal lymphatic capillaries, on the other hand, being empty and collapsed[6] are not so easily penetrated by the needle and hence not so frequently or extensively filled. It is conceivable that they do become filled with the solution but in the absence of lymphostasis any dye injected directly into the capillaries is so rapidly removed that it is not visible by the method which we employed.

It has been shown that in most types of edema, regardless of cause, lymphatic capillaries are wide open and distended with the edema fluid.[2, 7] Yet in this study patterns of

types 3 and 4 were observed with no significantly greater frequency in extremities edematous from acute thrombophlebitis and congestive heart failure than in normal extremities. In extremities edematous from chronic venous insufficiency patterns of type 3 were observed only rarely except in patients whose symptoms were of more than 10 years' duration, and it is known that lymphatic incompetency is occasionally a sequel to venous insufficiency of long standing.[8] In lymphedema praecox, however, in which the primary condition is incompetency of the lymphatic system,[5] patterns of types 3 and 4 were observed as frequently in the early stages as in the more chronic stages and irrespective of whether or not edema was present when the tests were performed. In fact, we, and also Kinmonth and Taylor,[5] have observed rather extensive patterns of lymphatic capillaries in the apparently normal and non-edematous legs of some patients with unilateral lymphedema praecox. It seems, therefore, that mere distention of lymphatic capillaries does not predispose to their ready demonstration after an intracutaneous injection unless there is also a factor of incompetency or lymphostasis.

Inconsistent with this reasoning were the results in patients with nephrotic syndrome, for 25 per cent of the injections into the edematous extremities of nephrotic patients resulted in patterns of types 3 and 4. This is considerably more than in normal extremities but considerably less than in extremities affected by lymphedema. There is no reason to believe that lymphatic incompetency is a factor in nephrotic edema and, in fact, McMaster[2] has demonstrated that lymph flow is markedly increased in the skin of extremities edematous from nephrosis. It is difficult to explain why the capillaries of an apparently competent lymphatic system become filled so frequently in nephrotic edema but fail to fill so readily in extremities with other types of edema, unless it is due to the fact that all of the extremities with nephrotic edema that were studied were massively edematous at the time of the injections while many of the extremities in the other categories were not edematous or only slightly so when the injections were made. Unfortunately we did not have the opportunity to repeat the injections in patients with nephrosis to determine whether or not lymphatic capillaries could be demonstrated as readily after edema had subsided.

The failure to demonstrate patterns of types 3 and 4 in the cases of extremely chronic lymphedema praecox (74 and 23 years' duration) may be due to obliteration of the cutaneous lymphatic capillaries by proliferation of fibrous tissue in the chronic stages of lymphedema.

Too little is known about the pathophysiology of lipedema and simple orthostatic edema and too few cases of edema due to hypoproteinemia and cirrhosis of the liver were studied to justify comment at this time.

The high incidence of islands demonstrated after injections into lymphedematous extremities tends to confirm McMaster's[9] opinion that they are indicative of lymphatic incompetency. McMaster[2] rarely found islands after injections into extremities with nephrotic edema, but described a high incidence in congestive heart failure. We have found just the opposite.

Summary

A method for demonstrating cutaneous lymphatic capillaries by injecting a fluorescent dye (riboflavin) intradermally is described. The patterns observed in the skin under ultraviolet light after such injections are classified as types 0 to 4, the former indicating no demonstration of lymphatic capillaries while the latter indicates maximal demonstration. Patterns of type 4 were not seen in normal extremities and only 1.5 per cent of the injections into normal extremities resulted in patterns of type 3. In contrast, 17 per cent of the injections into extremities with lymphedema showed patterns of type 4 and 44 per cent showed patterns of type 3.

Patterns of types 3 and 4 were observed much less frequently in extremities with edema owing to causes other than lymphedema. Only in nephrotic edema did the frequency of patterns of types 3 and 4 (25 per cent) approach that seen in lymphedema.

Certain of the data presented indicate that

xtensive filling of the lymphatic capillaries as in types 3 and 4) indicates lymphatic ncompetency and not just lymphatic disention. However, further observations are ecessary before the value of the fluorescent heal test in the differential diagnosis of eripheral edema can be definitely determined.

Summario in Interlingua

Es describite un methodo pro demonstrar utanee capillares lymphatic per medio del jection intradermal de un colorante fluorescente (riboflavina). Le configurationes observate in le pelle sub le lumine ultraviolette ost tal injectiones esseva classificate como ypos 0, 1, 2, 3, e 4. Le prime de iste typos habeva nulle demonstration de capillares lymphatic; le ultime habeva un demonstration maximal. Configurationes del typo 4 non esseva trovate in extremitates normal. Solmente 1,5 pro cento del injectiones in extremitates normal resultava in configurationes del typo 3. Del altere latere, 17 pro cento del injectiones in extremitates con lymphedema monstrava configurationes del typo 4, e 44 pro cento monstrava configurationes del typo 3.

Configurationes del typos 3 e 4 esseva observate multo minus frequentemente in extremitates con edema debite a causas altere que lymphedema. Un exception es le edema nephrotic. In illo le frequentia del configurationes typo 3 e typo 4 (25 pro cento) se approximava al frequenta de iste typos in lymphedema.

Certes del datos presentate indica que le extense plenamento del capillares lymphatic (typos 3 e 4) significa incompetentia lymphatic e non simplemente un distension lymphatic. Tamen, observationes additional es necessari pro determinar definitemente le valor del supra-describite test in le diagnose de edema peripheric.

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Peripheral Venoconstriction in Human Congestive Heart Failure

By J. Edwin Wood, M.D., Julius Litter, M.D. and Robert W. Wilkins, M.D.

A method for measuring venous "tone" in the limb segment of man in vivo was used to study the problem of cardiac decompensation. Venoconstriction was present in patients with heart failure and it tended to remit as the patients improved.

VENOCONSTRICTION has been suggested as an explanation for a variety of observations made on animals and humans suffering from cardiac decompensation.[1-5] We have used the method described by Litter and coworkers for measuring peripheral venous distensibility[6] to study this aspect of congestive heart failure in man. The method measures the increment of limb volume occurring in response to a known increment in local effective venous pressure. The experimental conditions were such that the starting point for each determination was a low, constant local effective venous pressure which had been rendered independent of central venous pressure. This characteristic of the method was important in that it allowed comparison of data obtained from different patients with widely divergent central venous pressures.

The observations here reported indicate that the peripheral veins of patients with congestive heart failure are constricted as compared with those of patients who have no cardiovascular disease and that this venoconstriction tends to remit with recompensation.

Methods

All patients were studied in the sitting position since orthopnea prevented some from lying supine. The forearm rather than the leg was studied as the edema of the lower extremities of some of the patients might have affected the results.

The subject was seated in a comfortable chair with his forearm inserted into a water-filled, variable-depth, limb-segment plethysmograph which was 16.5 cm. long. A 5 cm. wide arterial occluding cuff around the wrist was inflated to suprasystolic pressure just prior to each determination. Volume changes of the limb segment were recorded on a kymograph by a heated stylus attached to a Brodie bellows. The bellows was calibrated with known volumes of air introduced into the system. The patient's hand was supported by sand bags and the partially flexed elbow was supported by a rigid, padded block with two of its sides enclosed to prevent motion of the elbow. The forearm was placed at the level of the shoulder. A venous occluding cuff 12.5 cm. wide was placed around the upper arm. It was held firmly in place by adhesive tape and gauze. Great care was taken to prevent the cuff from exerting pressure on the arm in the uninflated state. Pressures in this cuff were controlled with a water manometer. Venous pressure was measured in the opposite arm, which was at the same level as the plethysmographic arm, either just prior to, or throughout, each experiment. Venous pressure related to the level of the plethysmographic arm is referred to as the *natural local venous pressure*. The plethysmographic water level was at least 5 cm. higher than the level of natural local venous pressure. Whenever possible, venous pressure was recorded in the supine position and related to the right atrium by the method of Lyons and associates.[7] When the patient was unable to assume a supine position, venous pressure was related to the right atrium by the method of Winsor and Burch.[8] Pressures related to the right atrium are referred to as the *venous pressure*. When this pressure exceeded 16 cm. of saline it was considered to be elevated.

The experimental procedure for obtaining peripheral venous distensibility was as follows: The plethysmographic water level was adjusted as noted above. Since external pressure around the forearm then exceeded the natural local venous pressure, the arterial inflow forced the local venous pressure to a level high enough to exceed slightly the applied external water pressure. The effective pressure (internal pressure minus external pressure) within the veins and their contained volume had then reached a *low*, constant and reproducible value. This pressure will be referred to as the *effective local venous pressure*. When measured directly, this value was found to be less than 1 mm. Hg. An equivalent starting point for each determination was then assured. The venous congesting cuff on the upper arm

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was inflated at 1 mm. Hg increments until the first small increase in forearm volume occurred. This cuff pressure (whatever it happened to be as related to atmospheric pressure) was called *cuff zero pressure*. Cuff pressure was then raised from cuff zero pressure to 30 mm. Hg pressure in 5 mm. Hg increments. Each of these pressure increments resulted in a volume increment of the forearm and as soon as a new forearm volume was reached the next 5 mm. Hg increment of pressure was introduced into the cuff. The total of the volume increments of the forearm segment venous system in response to the increase of 30 mm. Hg effective local venous pressure was thus measured, starting at an effective venous pressure of less than 1 mm. Hg. The volume of the forearm segment contained within the plethysmograph was obtained by subtracting the capacity of the plethysmograph with the forearm in place from its previously determined total capacity. The total forearm venous volume increase was converted to cubic centimeters per 100 cc. of tissue and is referred to as *venous distensibility*. A small distensibility was interpreted as representing relative venoconstriction and a large distensibility represented relative venodilatation.

Subjects

Twenty hospitalized patients with signs and/or symptoms of congestive heart failure during or prior to testing were studied on 33 occasions. The types of heart disease which caused the cardiac decompensation were distributed as follows: five hypertensive, three arteriosclerotic, four rheumatic, one syphilitic, five chronic pulmonary artery hypertensive, and two degenerative. The results of this study were essentially the same in all the types of heart disease studied. In 20 experiments the patients had elevated venous pressures while in 13 experiments the patients had normal venous pressures. Six of these 13 had some clinical evidence of cardiac failure while the rest appeared free of failure on clinical evaluation at the time of the experiment. In general, the patients with heart failure in the normal venous pressure group were not as severely incapacitated as were those in the elevated venous pressure group.

Another group of 10 hospitalized patients with no cardiovascular disease but of roughly comparable age and sex distribution was studied. These patients were considered to be normal controls, though they did suffer from a variety of diseases. The results obtained in this group were similar to those obtained in other studies carried out on the lower limbs of supine normal young male subjects.[6]

Results

The peripheral venous distensibility in patients with heart failure who had elevated venous pressures averaged 2.9 cc. per 100 cc. of forearm with a standard deviation (S.D.) of ±0.6 cc. Venous pressures in this group ranged from 17.0 to 38 cm. of saline. There was no apparent correlation between the level of the venous pressure and the degree of venoconstriction. The values obtained in those patients who had definite clinical evidence of decompensation, but normal venous pressures averaged 3.2 cc. per 100 cc. of forearm with a S.D. of ±0.6 cc. Patients with heart disease, but no evidence of failure at the time of the study, averaged 4.4 cc. with a S.D. of ±0.9 cc. Finally, the patients who had no cardiovascular disease had an average value of 4.4 cc. per 100 cc. forearm with a S.D. of ±0.4 cc., (fig. 1).

Four patients from the group with heart failure and elevated venous pressure were

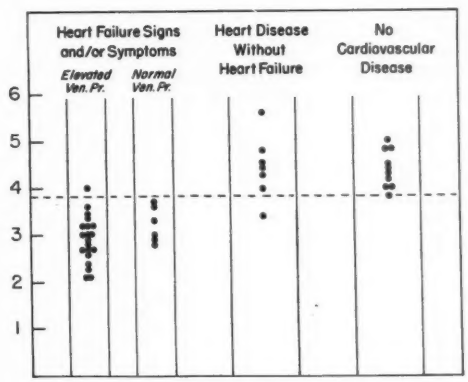

Fig. 1. Venous distensibility observations (cc. per 100 cc. forearm, ordinate) under various clinical circumstances. Dotted line indicates lower limit of control group.

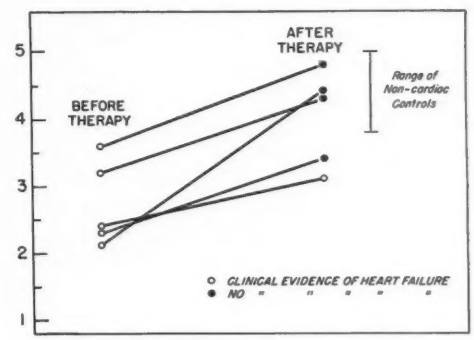

Fig. 2. The effect of therapy on venous distensibility (cc. per 100 cc. forearm, ordinate).

studied again after recompensation and their venous distensibility rose from 2.3 cc. to 3.4 cc., 2.1 cc. to 4.4 cc., 3.6 cc. to 4.8 cc., 3.2 cc. to 4.3 cc. per 100 cc. of forearm, respectively. One patient with elevated venous pressure was improved by therapy and venous distensibility rose from 2.4 to 3.0 cc. per 100 cc. of forearm (fig. 2).

Discussion

These studies indicate that the peripheral venous systems of patients with congestive heart failure are less distensible than those of patients without cardiovascular disease. However, there was no apparent relationship between the degree of venoconstriction and the magnitude of venous pressure elevation in the congestive heart failure patients. Indeed, patients with other signs of cardiac decompensation, but normal venous pressure frequently though not invariably showed decreases in distensibility of the same order of magnitude as those observed in patients with elevated venous pressures. This decreased distensibility or venoconstriction tended to remit as the patient improved and in fact it often returned to the range of control values after successful therapy. Thus the status of the peripheral veins could be roughly correlated with the overall clinical status of an individual patient's decompensation.

The evidence presented establishes a firm basis for the belief that peripheral venoconstriction occurs in patients with congestive heart failure. However, whether or not this peripheral venoconstriction is also generalized cannot be determined by this method. One can state that at a given venous pressure within the range of the pressures utilized for this study (0 to 30 mm. Hg) the contained volume of the peripheral vein system in congestive heart failure patients was less than that in normal subjects. These studies do not suggest a causative mechanism for the observed venoconstriction, nor do they clarify its relationship to the numerous other physiologic responses to the failing heart.

Summary and Conclusions

A method for the measurement of venous distensibility which effectively isolates the peripheral venous system from the influences of central venous pressure changes has been applied to the problem of human congestive heart failure.

Two groups of patients with heart failure were studied. One group was composed of patients who had elevated venous pressures and the second consisted of patients with normal venous pressures. Some of the patients were restudied after improvement occurred in the congestive state. A group of patients who had heart disease but were not in failure at the time of testing were studied.

A control group composed of hospitalized patients who had no cardiovascular disease was also studied.

The patients with heart failure had peripheral venoconstriction as compared with the control patients. This decreased venous distensibility returned toward or to normal as compensation of the heart failure occurred. Venoconstriction was observed in heart failure patients who had normal peripheral resting venous pressures as well as in those with elevated peripheral venous pressures.

Summario in Interlingua

Un methodo pro le mesuration del distensibilitate venose, que isola efficacemente le peripheric systema venose ab le influentia del variationes in le pression venose central, esseva applicate al problema del congestive disfallimento cardiac in humanos.

Esseva studiate duo gruppos de patientes con disfallimento cardiac. Un del gruppos consisteva de patientes con elevate pressiones venose. Le patientes del secunde gruppo habeva normal pressiones venose. Alicunes del patientes esseva restudiate post que illes habeva attingite un melioration de lor stato congestive. Esseva studiate un gruppo de patientes con morbo cardiac, non in stato de disfallimento al tempore del tests. Etiam un gruppo de controlo esseva studiate, consistente de patientes hospitalisate qui non habeva morbo cardiovascular.

Le patientes con disfallimento cardiac habeva venoconstriction peripheric in comparation con le patientes de controlo. Iste reducite distensibilitate venose retornava verso o usque a

alores normal in tanto que compensation del isfallimento cardiac esseva effectuate. Venoonstriction esseva observate in patientes de isfallimento cardiac qui habeva normal eripheric pressiones venose in reposo e etiam n patientes qui habeva elevate peripheric ressiones venose.

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Studies on the Control of Hypertension

VI. Some Evidence for Reversal of the Process During Hexamethonium and Hydralazine Therapy

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Because doses of antihypertensive agents necessary to control human arterial hypertension at relatively normotensive levels were observed to decrease with time, records of all patients in our series receiving oral hexamethonium chloride and hydralazine (but no other drugs) were analyzed (114 cases). After two years of therapy, those patients maintaining average diastolic pressures below 100 mm. Hg were found to require considerably less methonium ion while those unable or unwilling to control their pressures to this degree needed approximately their initial doses. Further decreases in drug requirements for the well-controlled group occurred after three years. Ten were able to discontinue all medication eventually and nine others needed only smaller doses of hydralazine; in these reversal of secondary changes was sometimes observed. Prolonged, continuous and adequate drug therapy is apparently associated with a change in the basic process producing hypertension.

AFTER the first consistent successes in chronically lowering markedly elevated human diastolic pressure to normal or nearly normal values by autonomic blockade plus oral hydralazine,[1, 2] interest was aroused as to the permanence of the change or lack of it. Although the side effects of therapy gradually dwindled in a manner reminiscent of the tolerance characteristic for methonium compounds,[3] no tolerance to the antihypertensive effect of the combined treatment has been observed after four years. On the contrary, a progressive diminution in drug requirement has frequently been observed.[4] Moreover, after varying periods of induced normotension, some patients, including an occasional one who originally had severe diastolic hypertension, have been gradually able to diminish and eventually to discontinue treatment entirely, without re-elevation of blood pressure. To ascertain the magnitude of such trends, the dosage and blood pressure data for our patients orally treated with hydralazine and hexamethonium chloride have been tabulated. This paper indicates the overall results and discusses in some detail those patients who no longer require autonomic blocking agents. Because generalized vasospasm, and not secondary atherosclerosis, was being affected by the drugs, the severity of the disease encountered is considered mainly in terms of blood pressure.

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Method

Every patient with high blood pressure discharged from Barnes Hospital between August of 1951 and May of 1954 after treatment by us with both oral hexamethonium chloride and hydralazine, but no other antihypertensive agent, was included in the study, provided that adequate daily follow-up data were available for at least one year, that there was no evidence of delayed hydralazine toxicity[5] or other intercurrent condition, and that other vasoactive drugs, particularly the Rauwolfia or veratrum alkaloids and newer ganglionic blocking agents, were not added to the regimen during the period in question. Unfortunately, a considerable number of the more severely hypertensive patients had to be removed from the series because of replacement of hexamethonium with pentapyrrolidinium ion or the addition of reserpine. Of the 114 individuals who fulfilled the criteria, 59 were white males, 13 were Negro, and 29 were ward patients. The average age was 46 with a range from 24 to 65 years. Although nine had been surgically sympathectomized at the time of first entering the hospital, none was following any effective antihypertensive regimen other than sodium restriction.

The pretreatment control diastolic pressure taken with the patient at rest in bed exceeded 100 mm. Hg

n all instances and it was felt that both ganglionic blockade and hydralazine were needed to produce normotension. The pretreatment value for each patient was the mean of all supine readings taken by nurses at four hour intervals day and night in the hospital before any drugs were given. The mean number of measurements averaged for each patient was 18. A minimum of 10 readings were available except in the cases of five individuals admitted as emergencies because of signs of cerebral edema and a diastolic pressure greater than 150 mm. Hg.

Fundoscopic examination, urinalysis and a determination of the level of nonprotein nitrogen in the blood was carried out in all cases. Hemorrhagic and/or exudative retinitis was observed in 39, of whom 10 showed edema of the optic nerve as well. Twenty-eight had 1 to 4 plus albuminuria and 26 more a trace of protein in their urine. Thirteen were azotemic with an average of 41 mg. of nonprotein nitrogen per 100 ml. of plasma.* The mean excretion of intravenously injected phenol red within 15 minutes was 19.9 per cent in the 102 tests for which the urine volume was adequate. In 32 of the 66 instances when a sodium amytal release test was performed, the diastolic pressure remained above 90 mm. Hg, the minimum reading averaging 106 mm.

In the hospital, the average diastolic pressure was controlled with a constant dose of oral hydralazine at four-hour intervals and simultaneously a variable dose of oral hexamethonium chloride depending on the level of the sitting systolic pressure. Each patient obtained a sphygmomanometer and adequate instruction in its use. To each was explained his hospital regimen which he was instructed to continue at home. After discharge, each kept a daily record of his blood pressure and medication, which were collected upon his return. For 33 who required further regulation in the hospital, a check on the validity of the patient's own records was available; agreement was excellent. Pertinent laboratory data were gathered at suitable intervals by the same laboratory which made the pretreatment observations. No other drugs, dietary regimens, or therapy of any kind was employed.

Because of difficulty in grading the severity of the hypertensive process objectively, the patients were divided into three arbitrary groups solely on the basis of their pretreatment diastolic pressures, no account being taken of the presence or absence of serious secondary manifestations, such as congestive heart failure, cerebrovascular accident, coronary occlusion or renal functional impairment. Forty patients were in the so-called *mild* group with control diastolic pressures from 100 through 114 mm.; 41 were in the *moderate* group with pressures from 115 through 129 mm. and 33 were in the *severe* group with pressures from 130 through 180 mm. Hg.* The average pretreatment systolic pressures at rest for the three groups was 221, 193, and 179 mm. Hg respectively. A posttherapeutic diastolic pressure of 100 mm. Hg was arbitrarily chosen to divide each of the three groups into a so-called *controlled* and an *uncontrolled* subgroup. These pressures were calculated for the pair of weeks, exactly one month and one year after hospital discharge;† when they were

* The maximal normal level of nonprotein nitrogen in the blood after deproteinization by zinc hydroxide as used here (Somogyi, M.: Method for preparation of blood filtrates for determination of sugar. J. Biol. Chem. **86:** 655, 1930) is 26 mg. per 100 ml. The low value is due to removal of glutathione, ergothioneine, uric acid and perhaps other substances which are not precipitated by the more usual phosphotungstic acid procedure.

* For the sake of simplicity throughout the paper the italicized terms *mild*, *moderate*, and *severe* each designates a group of patients as defined in the text solely by their pretreatment diastolic pressures. This grouping is not to be confused with that previously used.[2] Of the patients here discussed nine had "moderate benign" stages of hypertension by the more usual classification, 66 had "severe benign" stages and 39 had "malignant" or "premalignant" stages, the latter with resting diastolic pressures above 120 mm. Hg and normal optic discs but with hemorrhagic and/or exudative retinitis and gravely impaired renal function. Similarly the italicized terms *controlled* and *uncontrolled* designates the subgroups of patients as defined in the text solely by their posttherapeutic diastolic pressure. For simplicity's sake in comparing values of both blood pressure and dosages, the period beginning one month after hospital discharge will several times be indicated as the initial posttreatment period to distinguish it from the periods beginning 1, 2 or 3 years following discharge.

† The blood pressure and the dosage of medication immediately before hospital discharge is an unfair base of comparison for the follow-up data since the period of control is brief and often does not represent a steady state. Diastolic pressure and drug intake for the last 48 hours in the hospital, for the first week at home and for the pair of seven day periods beginning exactly one and two months after discharge were calculated for a considerable number of patients. The first two were different from each other and from the last two, which, on the other hand, were quite similar. Using a fortnight instead of a week was carefully checked and found to be no more reliable; seldom was the variation between two consecutive weeks more than 10 per cent with respect either to blood pressure or drug intake. On this basis, the seven-day period, exactly one month following discharge from the hospital, was used to obtain the initial posttreatment blood pressure and dosage levels. Since warm weather lowers both the blood pressure and the hexamethonium requirement, only yearly follow-ups obviated seasonal bias and hence were considered worthwhile.

TABLE 1.—*Pretreatment Diastolic Pressure and Severity of Hypertension Compared with Diastolic Pressure and Drug Requirement after a Month and a Year of Treatment*

Group	Subgroup	No. of Patients	Pretreatment					After a Month of Therapy			After a Year of Therapy		
			Diastolic pressure	Retiniti	Albuminuria	Azotemia	15 min PSP % excreted	Diastolic pressure	Methonium	Hydralazine	Diastolic pressure	Methonium fraction	Hydralazine fraction
			mm. Hg					*mm. Hg*	*Gm./day*	*Gm./day*	*mm. Hg*		
Mild	Controlled	33	107 ± 5	0	0.39	0	25	90 ± 9	1.93 ± 0.70	0.45 ± 0.18	89 ± 7	0.64 ± 0.44	0.83 ± 0.30
	Uncontrolled	7	110 ± 6	0	0.29	0	24	101 ± 6	2.37 ± 0.76	0.55 ± 0.21	102 ± 1	0.91 ± 0.23	0.90 ± 0.32
Moderate	Controlled	27	121 ± 4	0.46	0.50	0.08	18	92 ± 2	2.30 ± 0.84	0.53 ± 0.17	92 ± 7	0.81 ± 0.45	0.89 ± 0.40
	Uncontrolled	14	123 ± 4	0.21	0.36	0.14	21	106 ± 6	2.21 ± 0.95	0.52 ± 0.11	108 ± 6	0.87 ± 0.12	0.99 ± 0.44
Severe	Controlled	19	143 ± 15	0.58	0.68	0.37	13	93 ± 3	1.77 ± 0.81	0.53 ± 0.21	90 ± 7	0.80 ± 0.52	0.99 ± 0.47
	Uncontrolled	14	146 ± 4	0.57	0.64	0.21	16	107 ± 5	2.50 ± 0.90	0.67 ± 0.28	110 ± 10	1.10 ± 0.52	1.02 ± 0.45

The two left hand columns designate the range of diastolic pressure before therapy and after a year of treatment respectively, as discussed in the second footnote. The third column shows the number of patients in each of the six subgroups. The following five columns indicate the pretreatment severity of the hypertension in each subgroup. The diastolic pressure is defined in the text. The figures in the columns headed with *Retinitis*, *Albuminuria* and *Azotemia* represent the fraction of individuals in each subgroup who had hemorrhagic or exudative retinitis, albuminuria, and azotemia respectively; the excretion of phenol red (PSP) is in terms of the mean percentage of dye appearing within 15 minutes of intravenous injection when the urine volume was adequate. The next three columns list the diastolic pressure and dosage data at one month after hospital discharge, obtained as described in the text. The final three columns tabulate similar information at one year after discharge; however, the dosages of drugs are expressed as ratios of the respective daily intakes, the basis of the ratio for each patient being the one-month figure for that individual. The number following ± throughout the table indicates standard deviation.

available similar two-year and three-year follow-up analyses were obtained. The individual values for each patient were gotten by averaging either 35 or 28 recorded blood pressure readings and dosages of each drug, depending on whether the patient took his medicine four or five times a day. Each of the figures for a group or subgroup cited in the text or in a table is the mean of the individual values for all the patients involved. Over 20,000 separate measurements of blood pressure were analyzed. Because of the variation in initial dosage from patient to patient, the percentage change was determined at annual intervals. Hence the follow-up hexamethonium and hydralazine intakes are expressed as ratios, being the daily grams ingested 1, 2, and 3 years after discharge from the hospital, divided by the daily grams ingested one month after discharge. Patients were not included in the figures anytime subsequent to discontinuation of one or both drugs, unless permanent normotension had been achieved.

RESULTS

After a month of treatment the average daily intake of oral hexamethonium chloride was 2.11 with extremes of 4.80 and 0.63 Gm. The dose was less than 1 Gm. per day in only six cases of which two were azotemic and one a sympathectomized patient. The comparable mean dose of oral hydralazine was 0.52 with extremes of 1.24 and 0.13 Gm. per day.

Table 1 indicates that the lower the pretreatment diastolic pressure the greater the likelihood of prolonged post-treatment *control*. Even in the *severe* group, however, the majority had diastolic pressures less than 100 mm. Hg after a year of therapy. In all three of the *controlled* subgroups a similar or lower diastolic pressure was maintained by less autonomic blocking agent after a year than initially,* but only an equivocal decrease in hydralazine ingestion occurred. The diminution in use of both drugs was greatest for the *mild* group. In contrast, there was no change in dosage or diastolic pressure for any of the three *uncontrolled* subgroups.†

* The diminution and eventual discontinuation of hexamethonium chloride is an automatic process dependent only on the patient's dosage schedule whereby the full dose is taken for a sitting systolic pressure over 140 mm. Hg; half of a dose for a pressure between 130 and 140 mm. and a fourth of a dose for a pressure between 120 and 130 mm. There is no comparable automatic decrease in the dose of hydralazine since the regimen calls for a constant intake until it is reduced by the physician.

† Most individuals in the *uncontrolled* subgroups either refused to increase their doses or were not urged to do so because of the presence of azotemia, old cerebral vascular accident or other secondary atherosclerotic complications. A few were deliberately maintained on their initial doses in order to observe whether or not their moderate or mild hypertension diminished. Sufficient doses have usually resulted in control.

TABLE 2.—*Comparison of Dosage and Blood Pressure, Early in Treatment and After Two Years for Seventy-Eight Patients and After Three Years for the Thirty-Seven Patients*

Group	Subgroup	No. of Pts.	Pretreatment, Diastolic Pressure, mm. Hg	Data After a Month of Therapy			Data After 2 & 3 Years of Therapy		
				Diast. Pressure, mm. Hg	Meth., Gm./day	Hydral., Gm./day	Diast. Pressure, mm. Hg	Meth., Gm./day	Hydral., Gm./day
Two Year Follow-up									
Mild	Controlled	28	107	90	1.97	0.46	85	0.37	0.58
	Uncontrolled	5	113	97	2.47	0.48	104	0.88	0.96
Moderate	Controlled	21	121	94	2.55	0.60	89	0.69	0.68
	Uncontrolled	8	123	106	2.56	0.54	108	1.06	0.85
Severe	Controlled	11	148	98	1.90	0.46	92	0.76	1.07
	Uncontrolled	5	136	110	2.67	0.65	111	0.93	0.77
Three Year Follow-up									
Mild	Controlled	12	105	87	2.21	0.54	85	0.42	0.58
	Uncontrolled	3	114	98	2.73	0.50	103	0.84	0.77
Moderate	Controlled	8	121	92	2.77	0.57	88	0.31	0.41
	Uncontrolled	5	123	106	3.03	0.54	108	0.96	0.75
Severe	Controlled	5	150	95	1.63	0.43	90	0.60	0.71
	Uncontrolled	4	136	108	2.96	0.63	105	0.69	0.81

Every patient for whom adequate data were available has been included in this table which is similar to table 1. Since the patients were all included in the first table it was not felt necessary to retabulate any indices of the severity of the hypertension beyond the mean diastolic pressure. The agreement between the pretreatment diastolic pressures in the two tables is a measure of how closely the smaller numbers of patients in table 2 resembles the corresponding parent group in table 1.

Choosing the data in another manner and considering only the *controlled* subgroups, 7 of 19 in the *severe* group, 9 of 27 in the *moderate* group and 13 of 32 in the *mild* group required less than half the initial post-treatment dose of methonium after a year. Two, 3 and 6 patients respectively needed less than a fourth of their blocking agent; and 1, 1, and 5 less than an eighth.

The first part of table 2 gives comparable results after two years of therapy for the 78 patients on whom adequate records are available. A downward trend of diastolic pressure in all three *controlled* subgroups is obvious. There is a further decrease in the hexamethonium requirement which is particularly evident for *controlled* patients of the *mild* group, 28 of whom required an average of only 37 per cent of their initial dose of blocking agent. There is a similar, but less marked decrease in the dosage of hydralazine.

The second part of table 2 lists the values for the 38 patients whose records are available for three years. The small numbers reduce the significance, but the previously mentioned two-year trends can be seen. It appears that the *uncontrolled* subgroups, unlike their *controlled* counterparts, had no definite change in diastolic pressure or dosage of drugs after two and three years.*

* Ten patients in the *moderate* and *severe* groups were dropped from the series after completing one or two years of therapy because pentolinium tartrate was then substituted for hexamethonium chloride. Three had been *controlled* but side effects were bothersome. For them the same degree of control continued with little amelioration of symptoms after the substitution. Their mean diastolic pressure on a daily average of 1.52 Gm. of hexamethonium chloride had been 88 mm. Hg and on 0.39 Gm. pentolinium tartrate was 91 mm. Hg. In 7 of the 28 patients in these two groups who had not been *controlled* at the end of one year, primarily because of excessive side effects, the change in regimen was made in an effort

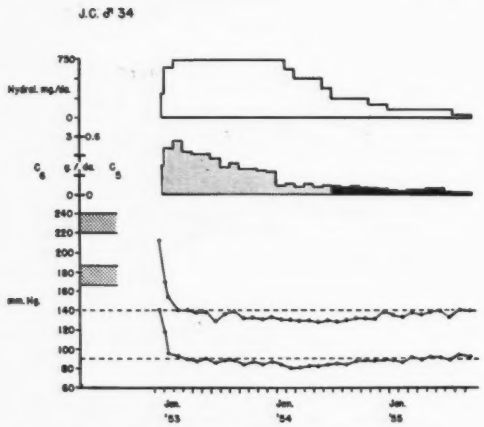

FIG. 1. Blood pressure and oral medication for a 34 year old white male with a malignant stage of hypertension. The range of pretreatment blood pressure is indicated by cross-hatching. The bar graphs indicate the drug intake, the open area representing hydralazine, the dotted hexamethonium (C_6), and the solid pentolinium (C_5). Note that the scale is different for the two methonium compounds since the second is approximately five times more potent than the first.

The change in blood pressure and medication with time are indicated in figure 1 for a single patient, typical in everything except the more than average severity of his hypertension. Before treatment, he had hemorrhagic and exudative retinitis with papilledema, a resting diastolic pressure of 140 mm. Hg in the hospital, 4 plus albuminuria and 10 per cent excretion of intravenously injected phenol red in 15 minutes. His daily oral medication, one month after hospital discharge, was 2.71 Gm. hexamethonium chloride and 0.75 Gm. hydralazine. At one year, the dose of blocking agent was 1.19 Gm. hexamethonium chloride and at two years it was 0.06 Gm. of pentolinium tartrate which is approximately equivalent to 0.30 Gm. hexamethonium chloride.[6] At three years it was 0.03 Gm. of pentolinium tartrate. The intake of hydralazine was 0.75, 0.15 and 0.025 Gm. at one, two and three years, respectively. The blood pressure has consistently remained below 140/90 mm. Hg and the 15 minute phenol red excretion has increased to 17 per cent.

Table 3 gives the individual data for those who were able gradually to decrease their doses of autonomic blocking agent and finally discontinue it while still maintaining an essentially normal diastolic pressure. Of the 19 patients, 10 had discontinued their hydralazine as well at the month indicated. All in the severe group had originally had electrocardiographic abnormalities, most had had albuminuria and half had had hemorrhagic retinitis. Considerable electrocardiographic evidence of disease, but few of the other changes beyond elevated diastolic pressure, had been present in the other two groups.

Eight patients of the 114 in the series died after an average of 26 months from the beginning of therapy. Three were not *controlled*, one year after starting treatment, because of intermittent discontinuation or insufficient dosage. In the other five the diastolic pressure had remained below 100 mm. Hg for a year; however, in 2 at least and probably in 2 others, therapy was lessened to the point of a re-elevation of blood pressure before death. A cerebrovascular accident was the terminal event in six. One died of cardiac rupture after myocardial infarction. The other, who had had a pretreatment diastolic pressure of 176 mm. Hg; hemorrhagic and exudative retinitis with edema of the optic nerves, and azotemia, died of renal failure after 30 months of treatment.*

The problem of patients passing from a *controlled* to an *uncontrolled* subgroup was never encountered in analyzing a patient's

to achieve control. The average of the mean diastolic pressures of four fell from 110 to 89 after they replaced a daily average of 3.77 Gm. of hexamethonium chloride by 0.82 Gm. of pentolinium tartrate. In the other three, however, no significant improvement could be discerned. Their average diastolic blood pressure only fell from 114 to 110 mm. Hg as they substituted a daily mean dose of 0.41 Gm. pentolinium tartrate for a daily dose of 1.99 Gm. hexamethonium chloride. The ratio of ingested pentolinium to hexamethonium ion approximated 1:5 which was previously reported[6] as being close to their relative antihypertensive efficacy.

* This patient was in fairly good health with well-controlled blood pressure in spite of slowly progressive azotemia (pretreatment nonprotein nitrogen of 61 mg. per 100 ml. of blood rising in 30 months to 103 mg.). Terminally, a severe gastrointestinal hemorrhage precipitated shock and uremia. Both kidneys together weighed only 105 Gm.

TABLE 3.—*Initial Intake and Length of Therapy in 19 Patients who Discontinued Methonium with a Comparison of Pre- and Post-Treatment Laboratory Data*

eth. at Mo.	Time Meth. Discont.	Fraction of Initial Hydral.	Diastolic Pressure		Optic Fundi		Albuminuria		% PSP in 15 Minutes		ECG		Index of Improvement
			Pre-treat.	Post-treat.	Pre-treat.	Post-treat.	Pre-treat.	Post-treat.	Pre-treat.	Post-treat.	Pre-treat.	Post-treat.	
g./day	*Months*		*mm. Hg*	*mm. Hg*									
1.66	34	½	147	79	0	0	Trace	0	15	15	Ischem & LVE	LVE	2
3.25	39	0	146	83	0	0	Trace	0	15	35	LVE	LVE	2
2.30	24	⅛	143	92	h & e	0	4+	0	10	17	LVE	Normal	3
2.34	12	0	130	77	h	0	0	0	25	—	LVE	LVE	1
2.38	27		142	83	2/4		3/4		18		4/4		2.0
1.21	24	¼	123	86	0	0	0	0	17½	20	Normal	Normal	1
1.25	13	⅕	123	96	0	0	0	0	15	—	LVE	—	0
3.27	31	0	120	92	0	0	0	0	25	10	Normal	Normal	−1
2.50	32	0	120	85	h	0	0	0	32	—	LVE	—	1
4.50	42	0	116	78	0	0	2+	Trace	7½	5	Normal	Normal	0
1.86	27	0	115	70	0	0	0	0	15	25	Normal	Normal	1
2.43	28		120	84	1/6		1/6		19		2/6		0.3
1.07	30	0	113	76	0	0	0	0	15	20	LVE	Improved	2
1.07	34	0	113	63	0	0	0	0	25	—	LVE	Normal	1
0.68	12	1	110	90	0	0	0	0	40	20	Damage	Normal	0
1.25	14	⅖	109	90	0	0	Trace	0	30	—	LVE	Improved	1
1.43	12	0	109	71	0	0	+	0	40	—	Normal	—	1
0.83	21	¾	108	91	0	0	0	0	5	15	LVE	LVE	1
2.08	39	0	108	84	0	0	0	0	20	25	LVE	Normal	2
0.89	30	⅛	106	98	0	0	0	0	35	—	Normal	Normal	0
1.11	15	⅔	105	89	0	0	Trace	0	25	25	LVE	Normal	2
1.16	23		109	84	0/9		2/9		26		7/9		1.1

Table 3 gives detailed data on 19 patients who without compromising their normotension have been able in periods from 12 to 39 months to diminish gradually and eventually discontinue the blocking agent (hexamethonium chloride, C_6) which was initially found necessary to control their hypertension. Four had pretreatment diastolic pressures of 130 mm. Hg or higher; 6 had pressures from 115 to 129 and 9 had pressures below 115. The next to the last patient in the table had been sympathectomized prior to drug therapy, which may explain the low initial dosage of hexamethonium chloride and the relatively high diastolic pressure at 30 months. Ten of these patients have been able to discontinue completely their hydralazine.

The first column indicates the average daily dose of hexamethonium after a month at home in the manner of table 1 and the text. The second column lists the number of months at which methonium medication was automatically terminated and the third indicates the dose of hydralazine at that time. The next five pairs of columns tabulate the control values and the values at the end of discontinuation of methonium for five laboratory evidences of the severity of hypertension. The pretreatment diastolic pressure is the previously discussed mean. The sixth and seventh columns show when hemorrhages (h) and/or exudates (e) were present in the optic fundi; the next pair, the presence or absence of albuminuria; the next pair, the 15-minute excretion of intravenously injected phenol red when the urine volume was at least 50 cc; and the final pair, electrocardiographic interpretation.

Abbreviations: ischem. = *myocardial ischemia*, LVE = *left ventricular enlargement*, normal = *within normal limits* and damage = *myocardial damage*. A final column has been added to summarize the changes in the fundi, urine, renal function and electrocardiogram. Any improvement between pretreatment and posttreatment values in these columns was counted as one. Many of the changes in any individual are not significant; however, the generalized nature of the improvement may be. The means for several of the columns are given underneath each of the three groups and, in several instances, are expressed as the number with an abnormality over the total number in the group.

records. Instances cited in the previous paragraph were discovered only after the terminal episode. Eight patients moved in the reverse direction from an *uncontrolled* to a *controlled* subgroup between the first and second years of therapy. Eighteen other patients who were *uncontrolled* after one year, and for whom a two year follow-up is available, did not change their status over this interval. Patients who keep adequate records for one year generally continue to do so. Of the 86 who began therapy more than 24 months ago, 78 have adequate two-year follow-up records while only eight have not communicated with us for three months.

There are an additional eight, currently normotensive, patients who have discontinued methonium medication, four of whom have discontinued hydralazine as well. They have not been included in the series because of the addition of Rauwolfia alkaloids to their regimens. All but one would have been in the *mild controlled* subgroup.

Discussion

This paper concerns itself with the relationship between blood pressure and drug dosage and how it changes with time. To avoid confusion only one antihypertensive regimen is considered. Laboratory and clinical data are treated more fully elsewhere.[7, 8] They are mentioned here only to demonstrate the severity of the hypertension.

The 114 patients were all considered to have serious hypertension. Their mean diastolic pressure at hospital rest was 123 mm. Hg. Almost half of the sodium amytal release tests did not result in diastolic normotension, and about half of the urinalyses revealed protein. Severe renal damage and hemorrhagic retinitis were common. In each case autonomic blockade plus hydralazine were either found or deemed necessary to achieve and maintain normal blood pressure. The data of tables 1 and 2 substantiate the longstanding clinical impression that a diminishing requirement for both blocking agent and hydralazine in order to maintain normotension occurs with time.[4] This lessened need for drugs suggests that the hypertension slowly alters to a stage less severe than at first. Increased sensitivity to the drugs, however, is not apparent in patients whose diastolic pressure remains distinctly elevated, even though it may have been lowered somewhat by therapy. Moreover, real tolerance follows discontinuation of the drug as in the previously reported case where the initial normotension effected by 1 Gm. of oral hexamethonium chloride daily could not be matched by less than 2.5 Gm. of oral pentolinium tartrate after treatment was once stopped and could not be approached by 4 Gm. of intramuscular pentolinium tartrate after the second discontinuation of autonomic blocking agent.[9]

There was no obvious pretreatment difference between those patients who were *controlled* by drugs and those patients who remained *uncontrolled*, yet after a year of therapy, 79 of the former needed an average of only 73 per cent of their initial blocking agent while 35 of the latter were still taking 97 per cent of it. At the end of two years, the percentages of blocking agent ingested by the two groups of patients were 57 and 99 respectively. Less definite were the comparable figures for hydralazine intake which were 89 and 96 per cent at one year and 71 and 86 per cent at two years.

Ten of 114 patients, including a pair in the *severe* group, were gradually able to discontinue all treatment without compromising their new-found normotension. Other laboratory evidence (table 3) for pretreatment cardiovascular and renal involvement substantiates the diastolic pressure as a measure of significant hypertension. Moreover, the trend toward normalcy noted in the objective tests following prolonged normotension suggests that lowering the blood pressure is worthwhile, since it allows some secondary manifestations of the pathologic process to reverse. Evidence of such regression has previously been observed for those severely hypertensive individuals who have the greatest opportunity to show this effect since they have the maximum pretreatment deviation from normal.[7]

It must be reemphasized that automatic and gradual withdrawal of drug therapy which accompanies prolonged normotension is very different in its overall result from sudden early discontinuation because of inconvenience or unpleasant side effects. The former results in apparent, although perhaps temporary, "cure" while the latter is usually fatal in sufficiently severe cases[7] or leads to a recrudescence of the original hypertension in milder ones.

The extent and direction of the systematic bias of the results is unknown. There is a tendency to lose both the best and the worst results to follow-up. The latter drop out to seek help elsewhere and the former are "cured" and need no help. Division into *controlled* and *uncontrolled* subgroups with 100 mm. Hg as the dividing line can be criticized. Depression of the diastolic pressure from 101 to 99 mm. Hg is hardly significant, whereas a depression from 150 to 101 may well be lifesaving. In order to be fully objective, however, it was felt necessary to be somewhat arbitrary.

Summary

One hundred and fourteen patients with hypertension of varying degrees of severity were followed closely during at least one year of carefully controlled therapy with an oral combination of hexamethonium chloride and hydralazine without other drugs. At the end of this period, 79 patients who had maintained diastolic pressures below 100 mm. Hg required only 73 per cent of their initial dose of blocking agent; whereas 35 whose hypertension had not been so reduced were still taking 97 per cent of their initial dosage. The 78 patients who were similarly followed for two years and the 37 who were followed for three years reinforced the suggestion that, following normotension or near normotension, the dosage of antihypertensive drugs diminished with time, whereas with less adequate control of blood pressure the required dosage remained unchanged. In 19 normotensive patients, this trend had extended to the point of complete discontinuation of hexamethonium chloride and in 10, to the discontinuation of hydralazine as well, without a recrudescence of hypertension.

Acknowledgment

We are indebted to Betty F. Perry for the extensive mathematic calculations.

Summario in Interlingua

Cento dece-quatro patientes con hypertension de varie grados de severitate esseva observate durante un anno o plus de un cautemente controlate therapia oral a chlorido de hexamethonium combinate con hydralazina. Nulle altere droga esseva usate. Al fin del periodo, 79 patientes qui habeva mantenite pressiones diastolic infra 100 mm Hg requireva solmente 73 pro cento de lor dose initial del agente blocator, durante que 35 patientes qui non habeva attingite un simile reduction de lor hypertension prendeva ancora 97 pro cento de lor dose initial. Septanta-octo patientes esseva similemente observate durante duo annos e 37 patientes durante tres annos. Le observationes de lor casos reinfortiava le notion que post le attingimento de normo- o quasi-normotension, le requirite doses del drogas antihypertensive se reduce in le curso del tempore, durante que in casos de minus adequate domination del pression sanguinee, le requirimento de dosage remane incambiate. In le caso de 19 patientes normotensive, iste tendentia attingeva le puncto del complete discontinuation de chlorido de hexamethonium. In 10 de ille casos etiam le hydralazina esseva discontinuate. Nulle de iste patientes experientiava un recrudescentia del hypertension.

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Pectoralis Minor Tenotomy and Anterior Scalenotomy with Special Reference to the Hyperabduction Syndrome and "Effort Thrombosis" of the Subclavian Vein

By JERE W. LORD, JR., M.D. AND PETER W. STONE, M.D.

Symptoms referable to the subclavian vessels or lowermost cord of the brachial plexus are frequently seen following repeated or prolonged hyperabduction of the arms. The sites of compression are thought to be the point at which these neurovascular structures emerge from beneath the pectoralis minor tendon and the interval between the clavicle and the first rib. Five patients presenting the hyperabduction syndrome have been subjected to pectoralis minor tenotomy and anterior scalenotomy with a good result in four cases, indicating the potential value of the procedure in this particular shoulder girdle syndrome.

IN 1945 Wright[1] described a syndrome characterized by neurovascular symptoms in the upper extremities following repeated and prolonged assumption of the position of hyperabduction. The postural attitude responsible for the symptoms was one in which the arms were brought together above the head with the elbows flexed. This position is frequently assumed in sleep but to lesser degrees is practiced in certain occupations such as grease pit mechanics and painters. With wider recognition of the syndrome it has been extended to include neurovascular symptoms resulting from lesser degrees of hyperabduction than that formerly described by Wright. The syndrome is to be differentiated from the allied causes of shoulder girdle symptoms such as the cervical rib, scalenus anticus and costoclavicular syndromes.

Wright[1] and Beyer and Wright[2] have described two potential sites of compression of the subclavian vessels and the brachial plexus in the hyperabduction syndrome. One site has been the point at which these neurovascular structures pass beneath the tendon of the pectoralis minor muscle and under the coracoid process. The second site of compression is the retroclavicular space between the clavicle and first rib which is diminished to a variable degree in hyperabduction. One of the authors (J. W. L., Jr.)[3] has previously reported upon experience with a "space making" operation in which a total resection of the clavicle is performed to prevent compression of the subclavian vessels and the brachial plexus between the clavicle and the first rib.

More recently, we have been impressed with the role of the pectoralis minor tendon and its division in the alleviation of vascular compression during hyperabduction. The subclavian artery and vein may be stretched and acutely angulated as they pass beneath the pectoralis minor tendon in the position of hyperabduction. With this factor in mind, a small group of cases with hyperabduction syndrome, refractory to conservative measures, have had section of the pectoralis minor tendon. At the same time, the anterior scalene muscle has been divided through a separate incision. The rationale for scalenotomy is found in the fact that this muscle with its attachment to the first rib serves to hold this rib in a relatively fixed position. By division of the scalene muscle it was felt that the rib might drop away from the clavicle thereby increasing the space between clavicle and first rib. An additional virtue of scalenotomy is the elimi-

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nation of pressure on the subclavian vein by the subclavius muscle and clavicle anteriorly and the scalenus anticus muscle posteriorly.

Operative Procedure

The patient is placed in the supine position on the operating table with a long, narrow sandbag in the interscapular region. The arm of the side to be operated is abducted to 90 degrees and placed on an armboard. Draping is then performed in such a manner that the arm may be moved freely during the course of the operative procedure, thereby enabling the operator to visualize the degree of compression of the axillary vessels and the brachial plexus by the tendon of the pectoralis minor.

Anterior Scalenotomy. A three inch transverse incision is made one half inch above the medial end of the clavicle. The incision is extended through the platysma muscle. The clavicular attachment of the sternocleidomastoid muscle is divided if the muscle is bulky and cannot be adequately retracted. The scalenus anticus muscle is identified and the phrenic nerve mobilized from its anterior surface and retracted. The muscle is then divided approximately 1 cm. from its attachment to the first rib. All bleeding points are ligated with fine silk or cotton ligatures. The operator introduces his finger into the interval between the clavicle and the first rib and evaluates the size of this space. The arm is then abducted to 180 degrees and also depressed downward and backward. The effect of these maneuvers upon the vessels and brachial plexus is noted. If there is marked narrowing of the space between the clavicle and first rib associated with a clinically positive costoclavicular maneuver, then a total claviculectomy is performed with removal of the periosteum. If there is adequate room, then the clavicular head of the divided sternocleidomastoid muscle is repaired with interrupted sutures of fine silk or cotton. The platysma and skin are closed with nonabsorbable sutures. The wound is not drained.

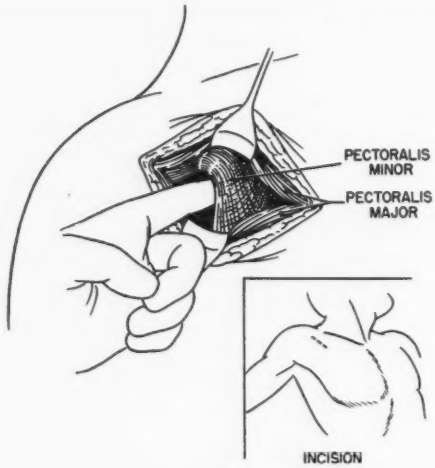

FIG. 1

Fig. 1. The pectoralis major muscle has been divided in the direction of its fibers. The operator's finger is behind the tendon of the pectoralis minor muscle. Inset shows approximate position and direction of skin incision for pectoralis minor tenotomy.

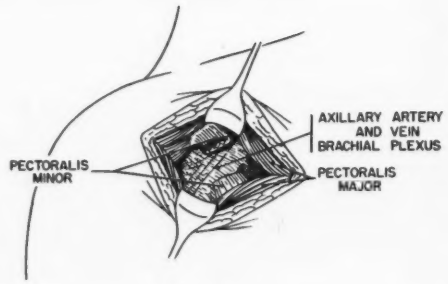

FIG. 2

Fig. 2. The tendon of the pectoralis minor muscle has been divided exposing the underlying axillary vessels and the cords of the brachial plexus.

Pectoralis Minor Tenotomy. A three inch oblique incision is made just below the coracoid process. The incision is deepened to the pectoralis major muscle which is incised and split in the direction of its fibers. A tape is passed around the tendon of the pectoralis minor muscle at the point of its insertion into the coracoid process. The arm is abducted to 180 degrees and the degree of stretching of axillary vessels and the brachial plexus under the pectoralis minor tendon noted. The tendon is then divided approximately one half inch from its point of insertion (figs. 1 and 2). The pectoralis major muscle and the skin are closed with interrupted nonabsorbable sutures. No drain is used.

Case Reports

Case 1. N. H., a 50 year old white female, had noted the right arm to be larger than the left for many years. Two months prior to admission there had been an episode of "paralysis" of the right arm which lasted for one week. During this time she was unable to write or perform other fine movements with the right hand. There had been a residual feeling of fullness in the right arm and intermittent tingling in the fingers of the right hand. She had also experienced pain in the right arm, shoulder and supraclavicular region.

Physical examination revealed the right arm to be 2 cm. greater circumferentially than the left arm. Three large veins were present on the inner aspect of the upper right arm and two prominent veins

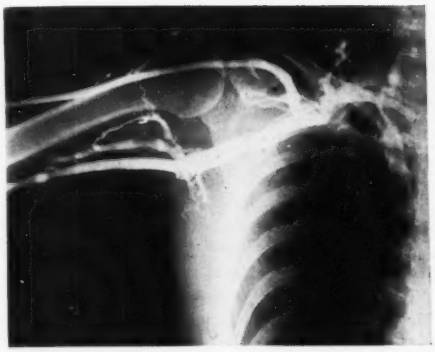

FIG. 3. (Case 1, N. H.) Venogram illustrating occlusion of the right subclavian vein. The cephalic vein enters below the point of obstruction.

were noted on the anterior right chest adjacent to the axilla. There were no prominent venous channels in the forearm. The brachial, radial and ulnar arteries were palpable. The right radial pulse was obliterated with hyperabduction of 135 to 180 degrees. The scalenus anticus and costoclavicular maneuvers were negative. X-ray films of the cervical spine were negative. A venogram revealed obstruction of the subclavian vein 2 cm. distal to the point of entry of the cephalic vein at the point where it passes under the subclavius muscle (fig. 3).

Anterior scalenotomy and section of the pectoralis minor tendon were performed on Jan. 5, 1953. During division of the scalenus anticus muscle a number of collateral venous channels were observed in the retroclavicular region. In addition a small nodule was excised from the upper outer quadrant of the left breast. This specimen was reported as cystic disease of the breast.

Immediately postoperatively the patient noted relief of pain in the arm and stated that "it felt quite different". The postoperative course was uncomplicated. When last seen on July 7, 1955 she had no complaints referable to the right arm and stated that she was able to use the extremity much better than preoperatively. Numbness and disability of the right hand had not recurred. The right arm remained 2 cm. larger than the left. The right radial pulse could not be obliterated with hyperabduction to 180 degrees.

Case 2. G. C., a 26 year old white male, gave a history of sudden onset of pain and swelling in the right arm and forearm while sweeping the floor two and one half years prior to the present hospital admission. The patient was hospitalized and under conservative treatment the pain and swelling subsided. Since this episode there had been recurrent attacks of swelling associated with an aching sensation in the arm and stiffness of the right hand. He was unable to abduct his right arm beyond 90 degrees because of diffuse pain. The patient reported that four years prior to the onset of the present illness he had had an infection of the right hand with complicating lymphangitis and lymphadenitis. However, following treatment at that time he had noted no residual symptoms resulting from the infection and did not relate his present symptoms to the prior infection.

Physical examination revealed prominent veins over the right upper arm and shoulder. The right arm and forearm were 1.5 and 0.75 cm. greater circumferentially than the left. All major arterial pulses were present in the right arm. Hyperabduction of the right arm resulted in obliteration of the radial pulse at 90 degrees. The scalenus anticus and costoclavicular maneuvers were negative. X-ray films of the cervical spine were negative. The patient was felt to have a thrombosis of the subclavian vein associated with the hyperabduction syndrome.

On Jan. 14, 1954 anterior scalenotomy and section of the pectoralis minor tendon were performed. Immediately postoperatively patient stated that his arm felt better and the hand had lost its stiffness. At the time of discharge from the hospital the aching sensation in the arm had completely cleared. He has continued to do well during the 17 months that he has been followed. The right arm and forearm continue to remain slightly larger than the left, and he states that he has noted weakness in the right arm when working with this extremity abducted to more than 90 degrees. Oscillometric studies performed on June 5, 1955 are shown in table 1.

Case 3. C. S., a 39 year old white female, was first seen in Aug., 1953. In May, 1953 she had noted redness and swelling of the right arm and a sensation of tightness in the muscles of the arm aggravated by exercise. She consulted a surgeon who reported erythema of the right arm and a one inch increase in its circumference on comparison with the left arm. The veins of the right arm were more prominent than those of the left. The blood pressure was essentially the same in both upper extremities. X-ray films of the cervical spine did not reveal a cervical rib. A diagnosis of scalenus anticus syndrome had been made and a right anterior scalenotomy was

TABLE 1.—*Oscillometric readings obtained in right and left arms with varying degrees of abduction (case 2)*

Degrees Abduction	Right Arm	Left Arm
0	2.0/100	1.5/80
90	2.5/120	2.75/80
180	2.0/60	1.25/60

The study was performed 5 months after right pectoralis minor tenotomy and anterior scalenotomy for the hyperabduction syndrome. Prior to operation the readings at 90 degrees and above were zero.

performed on July 31, 1953 without relief of symptoms.

When seen in August, the patient gave the additional history that when she combed her hair or abducted the right arm to 90 degrees or more in the performance of household duties, the arm became heavy and tired quickly. Abduction of the right arm to 90 degrees resulted in complete obliteration of the radial pulse. The scalenus anticus and costoclavicular maneuvers did not dampen the radial pulse. It was felt that the patient had a thrombosis of the subclavian vein and the hyperabduction syndrome. On Nov. 6, 1953 a division of the right pectoralis minor tendon was performed. Immediately postoperatively the right arm could be abducted to 180 degrees without dampening of the radial pulse. Examination one year following operation revealed that she had regained full use of the right arm. The heavy sensation and the easy fatigability had completely cleared. The right arm remained approximately 1 inch greater in diameter than the left, a residual of the subclavian vein thrombosis. A recent letter (July 21, 1955) stated that she had had no further trouble with the right arm.

Case 4. J. S., a 47 year old white male, had noted pain in both shoulders which radiated down the inner aspects of the arms to the hands for the preceding six months. The symptoms had increased in intensity and were worse on the right. He noted a definite relationship between the symptoms and the assumption of certain positions, particularly that of hyperabduction which he frequently assumed while sleeping. He was also known to have a moderate hypertension (170/110) for the preceding six months.

Physical examination was essentially negative except for a blood pressure of 168/100. The clavicles were prominent and markedly angulated in the anteroposterior plane in their middle thirds. The radial pulses were present bilaterally as were the other major pulses of the upper extremities. Abduction of the arms resulted in obliteration of the pulses at 135 degrees. Depression of the shoulders downwards and backwards (costoclavicular maneuver) resulted in complete obliteration of both radial pulses. The scalenus anticus maneuver was negative bilaterally. X-ray films of the cervical spine did not reveal a cervical rib on either side. Because of the more marked symptoms on the right side, it was decided to operate upon this side first and delay surgery on the left until a later date.

On Dec. 22, 1953 a right scalenotomy and division of the pectoralis minor tendon was performed. There was no thrombosis of the major artery or vein and the interval between clavicle and first rib appeared adequate. Postoperatively the right arm could be abducted to 180 degrees without dampening of the radial pulse. However, downward and backward depression of the shoulders continued to produce obliteration of the radial pulse. The postoperative course was unremarkable, but at the time of discharge from the hospital his symptoms were unimproved.

A report dated June 6, 1955 stated that the patient's symptoms persisted.[4] On Aug. 6, 1954 a right subtotal claviculectomy and excision of the subclavius muscle was performed by Dr. A. W. Hartman of San Antonio, Texas. The symptoms were relieved in the right arm and hand although he continued to complain of pain in the region of the lateral remnant of the right clavicle. On Jan. 28, 1955 a left total claviculectomy, excision of the subclavius muscle and anterior scalenotomy were performed by Dr. Hartman. The right clavicular remnant was also excised. Following these procedures it has been impossible to obliterate the radial pulse. However, he has continued to experience pain in both shoulders.

Case 5. A. S., a 44 year old white female, was first seen on Oct. 1, 1953 complaining of intermittent cyanosis, coldness and easy fatigability of the left hand. The patient stated that in February of 1953, six days following the spontaneous delivery of a full term stillborn infant, she had developed sudden pain, coldness and bluish discoloration of the left hand. The patient was treated with three stellate ganglion blocks at another hospital and the disability improved over a four month period. However, no further improvement had been noted in the following five months and the symptoms now occurred at frequent intervals. Physical examination revealed atrophy and weakness of the musculature of the left hand and slight cyanosis of the skin and nailbeds. Axillary, brachial, radial and ulnar pulsations were absent. The blood pressure taken on the right arm was 122/74 and unobtainable on the left. Oscillometric studies showed a deflection of 0.5 unit at the left wrist at 100 mm. Hg in contrast to a deflection of 2.5 units at the right wrist at an equivalent cuff pressure. The Landis test was interpreted as showing a marked element of vasospasm in both upper extremities.

On Nov. 19, 1953 the left axillary vessels were explored through a supra- and infraclavicular incision. The subclavian and axillary arteries were thrombosed from the medial aspect of the scalenus anticus muscle proximally to the mid-axilla distally. In view of the long segment of thrombosed artery (approximately 15 cm.) and the presence of feeble pulsations in the distal axillary artery, it was felt that resection of this thrombosed segment with graft replacement was not advisable. Section of the pectoralis minor tendon and anterior scalenotomy were performed to obviate additional trauma to the artery by these structures and to relieve as far as possible structural interference with the collateral arterial circulation.

The patient has been followed-up for 20 months and has noted progressive improvement in the left

arm and hand. She still notices fatigue in the hand and forearm but only after prolonged use. The hands are equal in temperature and a faint radial pulse is palpable on the left. Oscillometric studies on July 21, 1955 revealed a deflection of 2.0 units in the right wrist and 0.5 units in the left wrist.

Discussion

The results of section of the pectoralis minor and anterior scalenotomy in this small series were good in four cases and a failure in one. Of the successful cases (cases 1, 2, 3 and 5), three presented a thrombosis of the subclavian or axillary veins. Although the symptoms may conceivably have resulted from venous thrombosis, the prompt relief and subsequent freedom from the preoperative symptoms indicate that the disability probably resulted from intermittent compression of the subclavian and axillary arteries. These patients (cases 1, 2 and 3) still present a slightly swollen arm, but this has resulted in no incapacitation.

The failure in case 4 was felt to result from selection of the incorrect operative procedure. Whereas the former cases represented the pure hyperabduction state, case 4 was a mixed syndrome exhibiting the costoclavicular as well as the hyperabduction syndrome. The former syndrome, originally described by Falconer and Weddell[5] is characterized by an extremely narrow interval between the clavicle and the first rib. Relief of subclavian vessel and brachial plexus compression in this condition requires the removal of the clavicle or the first rib. It is apparent as a result of the persistent symptoms and the presence of a positive test for the costoclavicular maneuver that the latter syndrome represented the major difficulty in this case, and the follow-up data confirms this view. This case has also resulted in the placement of a long, narrow sandbag in the interscapular region when the patient is placed on the operating table. The sandbag causes the shoulders to fall down and back so that the operator may better evaluate the size of the interval between clavicle and first rib.

The failure in case 4 further illustrates the importance of accurate preoperative diagnosis if the correct operation is to be performed. Shoulder girdle symptoms resulting from a cervical rib, a hypertrophic scalenus anticus muscle or a narrowed interval between clavicle and first rib must be differentiated from the true hyperabduction state. Frequently, a combination of two or more of these syndromes is encountered. Beyer and Wright have reviewed the diagnostic possibilities and their differentiation.

We have not encountered reports of combined pectoralis minor tenotomy and anterior scalenotomy for the hyperabduction syndrome in the literature. Dr. Frederick W. Cooper, Jr., of Atlanta, has informed us that he has sectioned the pectoralis minor tendon in three individuals with the hyperabduction syndrome and that the results have been excellent in each case.[6] He is of the opinion that scalenotomy is not necessary unless a concurrent scalenus anticus syndrome is present.

Summary and Conclusions

Neurovascular symptoms, secondary to intermittent compression of the subclavian and axillary vessels and the lowermost cord of the brachial plexus, are sometimes seen following repeated or prolonged hyperabduction of the arms. The primary site of neurovascular compression is thought to be the point at which the vessels and nerves emerge from beneath the pectoralis minor tendon. A secondary site of compression is the interval between the clavicle and the first rib. Five patients presenting the hyperabduction syndrome have been subjected to pectoralis minor tenotomy and anterior scalenotomy with gratifying results in four. It is felt that failure in one case may be attributed to the fact that the patient presented a combined hyperabduction-costoclavicular syndrome and a primary claviculectomy would have been a more satisfactory procedure. The good results in the patients with the pure hyperabduction syndrome suggest that the procedure may be of value in the operative treatment of this particular shoulder girdle syndrome.

Summario in Interlingua

Symptomas neurovascular, secundari a compression intermittente del vasos subclavie e axillar e del infime chorda del plexo brachial, occurre a vices post repetite o prolongate

hyperabduction del bracios. Nos opina que le sito primari del compression neurovascular es le puncto in que le vasos e nervos emerge ab infra le tendine del pectoral minor. Un sito secundari del compression es le intervallo inter le claviculo e le prime costa.

Cinque patientes exhibiente le syndrome de hyperabduction esseva subjicite a tenotomia del pectoral minor e a scaleniotomia anterior. Le resultatos esseva gratificante in quatro casos. Nos crede que le disfallimento in le ultime caso es attribuibile al facto que le patiente presentava un combinate syndrome hyperabductioso-costoclavicular de maniera que claviculectomia primari haberea essite un procedimento plus satisfactori. Le bon resultatos in le patientes con le pur syndrome de hyperabduction supporta le suggestion que le technica es possiblemente de valor in le tractamento operative de iste specific syndrome del cinctura scapular.

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Total Anomalous Pulmonary Return

An Analysis of Thirty Cases

By VINCENT L. GOTT, M.D., RICHARD G. LESTER, M.D., C. WALTON LILLEHEI, M.D. AND RICHARD L. VARCO, M.D.

Thirty cases of total anomalous pulmonary return have been collected and analyzed. The pathways of drainage and their embryologic development are discussed. The cardiac catheterization, electrocardiographic and radiologic findings are also presented. These laboratory data accompanied by the clinical findings seem to identify a recognizable diagnostic picture for this malformation. Finally, our attempts at surgical correction of this defect are briefly enumerated.

ALTHOUGH anomalous pulmonary return has usually been considered quite an uncommon defect in the past, this may be an inaccurate impression. The misconception probably stems in part from the casual attention it has aroused among surgeons treating cardiovascular malformations.

Winslow is credited with describing the first case in 1739.[1] The anomalous drainage in Winslow's case was reported to be only partial and it was not until 1868 that total anomalous pulmonary return was described by Friedlowsky.[1] In 1942, Brody[1] was able to collect from the literature only 102 cases of anomalous pulmonary drainage. Sixty-five of these were partial anomalous returns and 37 were total. Since Brody's collection of 37 cases, we have found only 49 additional cases reported in the literature.[2-5] The majority of these authors have reported one or two cases. Keith[5], however, collected 14 personal cases, and of these 13 were verified at postmortem examination.

The drainage of a single pulmonary vein or the veins from one lung into the right side of the heart has been reported more frequently in the past few years. It is an entity that is less likely to create serious clinical distress. In our experience, its association with an atrial septal defect has been frequent. This paper will discuss only the less common but more critical problem of total anomalous return. We present here 30 cases from the University of Minnesota Hospitals (fig. 1). Three of these cases were discussed previously by Levin[6], these cases having a drainage through a "persistent left superior vena cava" or left vertical vein.

Twenty-six of the 30 patients have had proved diagnoses of total anomalous pulmonary venous return, 23 at autopsy and 3 at surgery. In four additional cases the diagnosis was made after a thorough clinical evaluation. Thirteen of the autopsied cases had only an associated patent foramen ovale. An additional four had also a patent ductus arteriosus, and six had other kinds of associated major cardiac defects.

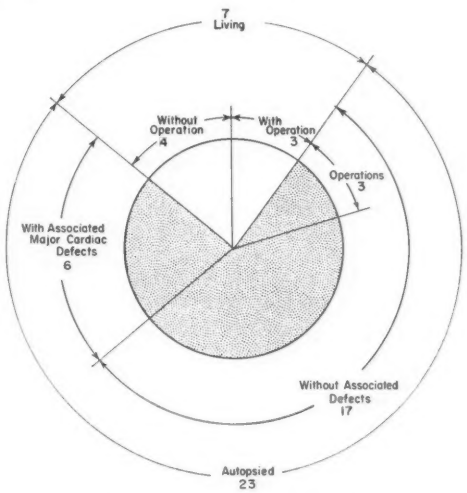

FIG. 1. Analysis of 30 cases of total anomalous pulmonary return.

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Dr. Gott is a National Heart Trainee, U. S. Public Health Service.

TABLE 1.—*Pathology in Six Cases with Associated Major Cardiac Defects of the Heart*

Pt.	Sex	Age	Drainage	Pathology
G. C.	M	25 days	I.V.C.	Very large interatrial defect making heart practically three chambered. This patient's brother died at 3 months with total anomalous pulmonary return
R. G.	M	5 wks	Anterior cardinal veins	Cor biloculare. Dextrocardia. Patient had persistent anterior cardinals and right and left pulmonary veins entering into respective cardinals
B. S.	M	3 days	R.A.	Left atrium is small piece of tissue without lumen. All pulmonary veins entering large right atrium. Single vessel leads from ventricle supplying lungs and neck
P. H.	F	3 mo.	R.A.	Absence of left atrium and left ventricle. Pulmonary veins enter right atrium. Aorta leaves right ventricle
M. R.	F	7 wks	L.S.V.C.	Dextrocardia. Pulmonary artery fibrotic at right ventricle. Interventricular defect with aorta over riding. All pulmonary veins into L.S.V.C.
M. S.	F	7 mo.	Abd. viscera	Pulmonary artery fibrotic at ventricle. Common ventricle. Large interatrial defect. Pulmonary veins empty into anomalous vessel that passes through diaphragm and terminates in pancreas and mesenteric veins

(See table 1.) In this group there were 17 males and 13 females.

As shown in figure 2, most of the patients did not survive the first three months of life. However, all seven of those now living are past infancy and one is a 33 year old woman, the mother of two children. We believe this is next to the oldest surviving patient recorded in the literature.

PATHOLOGY

The pathways of anomalous drainage in 26 proven cases are depicted in figure 3. The relative frequency of the various drainage sites corresponds closely to that described in those accumulated cases from the literature. Drainage via a "persistent left superior vena cava" is the most frequent pathway, the other two common sites being into the coronary sinus and directly into the right atrium. These routes of drainage have been noted in the great majority of cases; however other channels have been recorded rarely. Our series includes examples of most of these unusual drainage ways. It does not, however, include a case with drainage into the ductus venosus, of which three have been reported previously. An approximation of this tract, however, was found in one patient in whom the pulmonary veins emptied into the portal system (fig. 4). Two pathways of drainage in this series of cases have not previously been recorded in the literature. In M. S. the pulmonary veins from both lungs joined to form an anomalous channel that coursed caudad, penetrated the diaphragm and then subdivided into many small branches, terminating in and anastamosing with the veins of the pancreas and mesenteric plexus. This patient also had the multiple associated defects of situs inversus with dextrocardia, common ventricle, a large atrial septal defect and an atretic origin of the pulmonary artery. Despite the multiplicity of malformations this patient lived seven months. The second (R. G.) had drainage of the right and left pulmonary veins into the corresponding persistent anterior cardinal veins. This patient also had dextrocardia and cor biloculare.

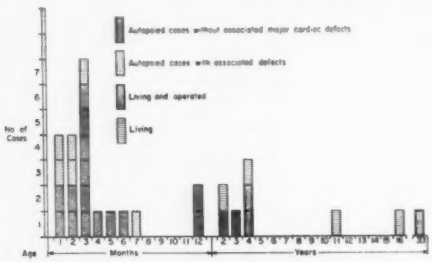

FIG. 2. Age distribution of patients.

In all the cases without associated major cardiac defects at autopsy, the right side of the heart was hypertrophied and the left side

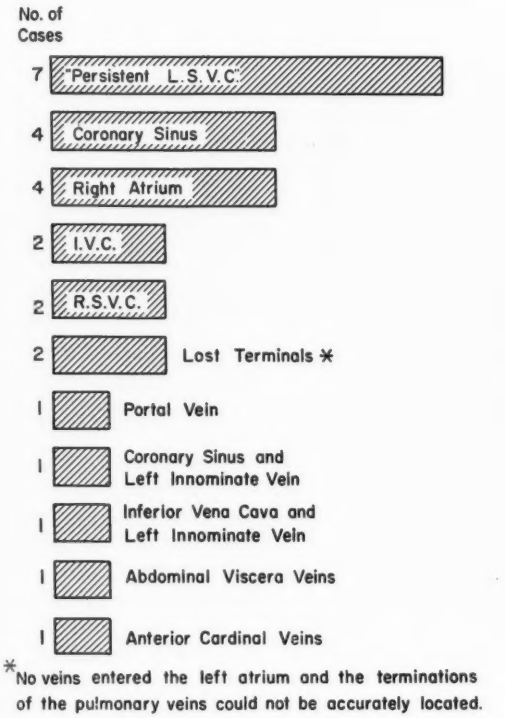
No. of Cases
7 "Persistent L.S.V.C."
4 Coronary Sinus
4 Right Atrium
2 I.V.C.
2 R.S.V.C.
2 Lost Terminals *
1 Portal Vein
1 Coronary Sinus and Left Innominate Vein
1 Inferior Vena Cava and Left Innominate Vein
1 Abdominal Viscera Veins
1 Anterior Cardinal Veins
*No veins entered the left atrium and the terminations of the pulmonary veins could not be accurately located.

FIG. 3. Drainage of 26 cases demonstrated at autopsy or at surgery.

FIG. 4. Anatomic arrangement in a case with drainage of the pulmonary veins into the portal vein.

atrophic. This may be of considerable importance in its surgical implications. On the venous side of the pulmonary circuit the dynamics of the lung require a low resistance flow system, or at least that there be no abrupt change in these values. Keith[5] stated that in his 13 autopsied patients the right atrium was 5 to 10 times the size of the left atrium, the right ventricle 3 to 5 times the size of the left ventricle, and the mitral valve was much smaller than the tricuspid valve.

Keith also pointed out, and this has been verified by our measurements, that the circumference of the anomalous pulmonary vessel is usually larger than the waist of the atrial appendage.

With complete drainage of the pulmonary and systemic veins into the right atrium, a right to left shunt is necessary for life. Before birth, both the ductus arteriosus and foramen ovale perform this function. After delivery, in the majority of cases, the patent foramen ovale or a larger atrial septal defect is the sole avenue for partial left-sided venous filling. As noted previously, in all 17 autopsied cases without major associated defects the foramen ovale was open to varying degrees.

EMBRYOLOGY

The lung develops as an outpouching from the ventral wall of the foregut, and the venous plexus covering the lung bud is thought to be part of the splanchnic plexus covering the foregut. Some authorities[7, 8] feel that the pulmonary venous plexus is gathered together into a common pulmonary vein which courses ventrally to tap the sinus venosus of the primitive heart. A recent and more strongly advocated theory[9-11] visualizes the pulmonary vein arising as an outpouching from the dorsal wall of the sinus venosus. This stem in turn communicates with the pulmonary venous

plexus. The opening of the pulmonary stem is initially in the center of the sinus venosus but with the formation of the septum the communication shifts to the left. The common pulmonary vessel is absorbed by the atrial wall so that its four subdivisions eventually enter the heart separately.

In the embryo the splanchnic plexus of the foregut communicates with all of the surrounding systemic and visceral veins (fig. 5). Thus at one stage in the normal development of the embryo there are communications between the venous plexus of the lung bud and the pre- and postcardinals, which eventually form the superior vena cava, innominate veins, azygos vein and coronary sinus. There are also communicating venous channels with the umbilical and vitelline veins which are the primordia for the portal vein, ductus venosus and inferior vena cava. Thus if there is a failure of connection between the pulmonary stem from the heart and the pulmonary plexus, other venous channels may persist to create this abnormality of total anomalous pulmonary return.

Theoretically, when the pulmonary veins enter directly into the right atrium, there has been a failure of the common pulmonary vein

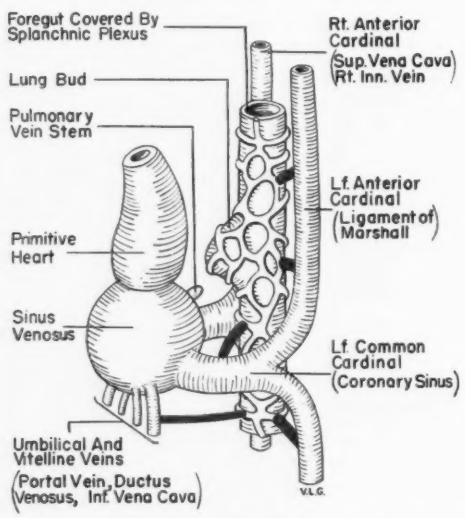

FIG. 5. Normal communications (in black) between plexus of lung bud and surrounding veins in the embryo heart.

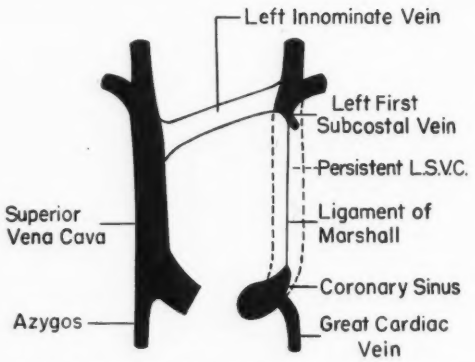

FIG. 6. The veins derived from the cardinal system of the embryo.

to be displaced to the left at the time of the development of the interatrial septum.

The most frequently encountered route of drainage in total anomalous pulmonary return is via the "persistent left superior vena cava." The use of this terminology has created some confusion in the literature because the vessel so named is not a persistent left superior vena cava or left anterior cardinal vein in the truest sense.[12] Embryologically the anterior cardinals join with the posterior cardinals to form the common cardinals or duct of Cuvier. The common cardinals in turn empty into the lateral recesses of the sinus venosus (fig. 5). On the right the anterior and common cardinal form the superior vena cava and its immediate tributaries. However, on the left the anterior and common cardinals regress leaving a proximal vestige as the coronary sinus (fig. 6). A truly persistent left superior vena cava communicates proximally with the coronary sinus and distally with the left innominate vein. Of the cases cited in the literature as having drainage via the left superior vena cava, none appear to drain in this fashion. The drainage is consistently cephalad into the left innominate vein and thence into the superior vena cava. In this paper, however, we shall use the term "persistent left superior vena cava" in order to be consistent with the previous literature.

CLINICAL FINDINGS

A history of cyanosis of a mild degree was present in most of our patients who at autopsy

TABLE 2.—*Cardiac Catheterization Data*

Groups	Pts.	Drainage	O_2 Content								Pressure	
			I.V.C.	S.V.C.	R.A.	R.V.	P.A.	Sys. A	Misc.	CAP.	R.V.	P.A.
Living without operation	H. S.	L.S.V.C.		22.3	21.7	21.4	22.1	21.4	L.S.V.C., 22.0	23.1	78/6	38/13
				97%	94%	93%	96%	92%	95%			
	T. H.	L.S.V.C.		16.1	14.6		15.3	14.3		17.4		
				93%	84%		88%	81%				
	J. M.	?		14.3	16.3	16.6	16.4	16.8	P.V., 17.6			
				82%	93%	94%	93%	93%	98%	17.7	54/0	54/0
	T. K.	R.A.	11.3		15.6			14.7		17.9		
			63%		87%			80%				
Living with operation	R. P.	S.V.C.	15.7	19.5	19.7		18.6	17.8	P.V., 19.1	20.1	109/0	46/15
			78%	97%	99%		93%	89%	95%			
	D. H.	R.A.		11.4	17.5	16.4	16.4	15.7				
				64%	98%	92%	92%	85.8%		18.0	40/0	40/20
	R. K.	R.A.		12.5	14.4			15.3	L.A., 15.5		34/2	34/10
				71%	82%			85.8%	86%			
Autopsied without assoc. defects	N. M.	C.S.	14.3		18.8	18.9		18.2		19.6	55/6	
			76%		96%	97%		91%				
	M. H.	C.S. & L.I.V.	6.9		16.7			16.6		18.3		
			38%		91%			91%				
	W. W.	C.S.	7.9		11.4	11.6		10.5		14.9	42/15	
			53%		77%	78%		71%				
	W. K.	L.S.V.C.	2.2		9.1			8.9				
			13%		52%			51%		17.4		
	L. P.	L.S.V.C.	3.3	2.2	13.4			12.2		17.3		
			19.4%	12.5%	77.6%			69%				
	B. D.	R.S.V.C.	9.0	12.8	13.9			12.8		18.4		
			48.9	68%	76%			68%				

were without associated major cardiac defects. The terminal patients had moderate to marked cyanosis. The systemic arterial saturation ranged from 69 to 93 per cent in those so tested. Although some degree of arterial desaturation is present by necessity in nearly every patient with total anomalous pulmonary return, in some cases clinical cyanosis may not be evident until late in the patient's life span. For this reason we agree with Edwards,[13] who feels that this malformation should be placed in the cyanotic group. Those, however, with partial anomalous return also have the potential for cyanosis. Most of them have a defect in the atrial septum, and may eventually develop pulmonary hypertension which, in turn, tends to induce a right to left shunt.

Fourteen of the 17 autopsied cases without associated defects exhibited during life a systolic murmur in the second or third left interspace. In three patients no murmur was recorded. The susurrations heard were attributed to the flow through the atrial septal defect during atrial systole with the additional possibility of a component due to turbulence in the pulmonary artery being induced by the increased minute flow.

Cardiac Catheterization

Thirteen individuals underwent cardiac catheterization. Four of these patients are living and it is presumed from the data that their major defect is total anomalous pulmonary return. The remaining nine patients had this diagnosis confirmed at the time of surgery or autopsy. The data are presented in table 2. A striking feature is the high oxygen saturation of the right atrial blood. In every instance except one it was equal to or higher than the oxygen saturation of the systemic arterial blood. These findings are unlikely to appear in any other congenital heart condition save for the example in which the catheter tip is placed immediately adjacent to an atrial defect.[14] This group exhibited some pressure increase in the right ventricle and in the pulmonary artery.

Two of the patients had on catheterization some evidence of pulmonary outflow tract obstruction. One of these (H. S.) is living without an operation. The other (R. F.) was successfully operated on. It is of interest that these two persons with pulmonary stenosis are the oldest individuals in the series, 16 years of age and 33 years old, respectively. Apparently the dampening effect on the greatly increased pulmonary flow by the stenotic pulmonary valve was of some value in retarding the onset of damaging pulmonary vascular changes.

Electrocardiogram

Twelve of the 17 patients without associated intracardiac defects had right axis deviation and seven demonstrated right ventricular hypertrophy. A high incidence of right bundle branch block has been reported with this defect.[2, 15] However, we found only one case that showed such a tracing.

Radiologic Examination

Of the 20 cases proven at autopsy or at surgery, without other significant cardiac defects, all but two underwent a conventional x-ray examination, including multiple films and fluoroscopy. Six patients were also examined by angiocardiography.

Several authors[5, 6] have referred to the "figure of eight" appearance (fig. 7) formed by engorged "left" and right superior vena cava above, and the bulk of the heart below. This

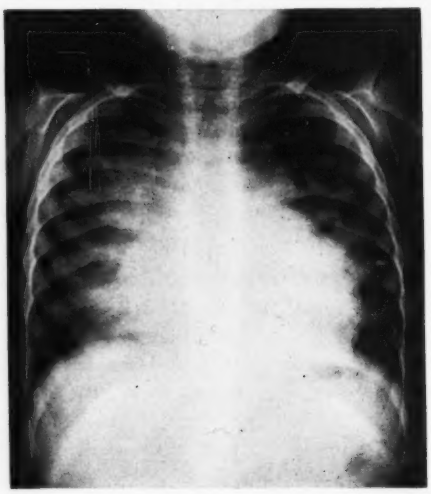

Fig. 7. Total anomalous return through "persistent left superior vena cava" demonstrating "figure of eight" configuration.

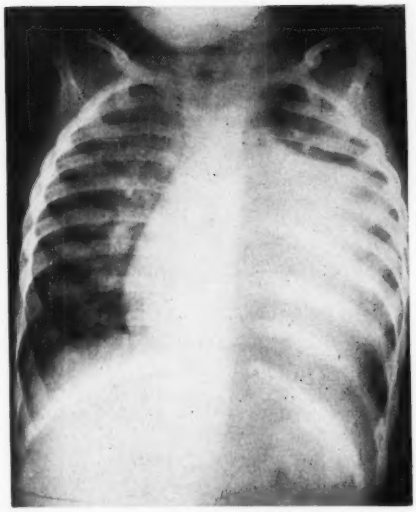

FIG. 8. Demonstration of "box-like" shape.

has come to be accepted as typical of this malformation. It should, however, be kept clearly in mind that this roentgen appearance is seen only in those cases in which the anomalous pulmonary vessels empty into a "persistent left superior vena cava." Unfortunately, not all of the patients even with this anatomic derangement will show this diagnostic form on the plain posteroanterior roentgenogram. In this group of 20 only three demonstrate well the "figure of eight". These have been reported previously by Levin and Borden.[6] This diagnosable group represents but half of the total number of persons with "persistent left superior vena cava."

All of the cases reviewed, with the exception of one who died at the age of 10 days, had a mild to marked increase in the pulmonary vascularity. In all the patients who survived three or more months, this was present to a marked degree.

Twelve of the 18 patients showed what we believe is a characteristic shape of the heart as viewed in the posteroanterior position. This typically, is a box-like appearance with an almost horizontal take off of the left border of the heart below the aortic arch. It should be in association with the increased vascularity just mentioned (figs. 8 and 9). This profile results from massive enlargement of the right atrium and ventricle, with the latter structure probably forming most of the upper left border of the heart. There is no left atrial enlargement.

While this appearance has not been emphasized in the literature it is not an original observation. Taussig's monograph[14] demonstrates a case showing this feature. Snellen[16] refers to a similar contour. In Keith's article[5] there are several tracings of roentgenograms which also depict this outline in some of the cases.

A review of the earliest angiocardiograms made on the first patients to undergo this procedure failed to reveal much of diagnostic aid. There was diffusion of the opaque medium within the heart after entry from the vena cava and, in one case, evidence of recirculation through the right side of the heart. We believe these examinations were probably inadequate technically.

Angiograms secured in a later series of three cases, however, show an appearance that we feel is typical for this disorder. These patients were all examined in the right posterior oblique projection. In two cases 70 per cent Diodrast and in one 70 per cent Urokon (1.2 to 1.5 ml. per Kg. of body weight) was injected as rapidly as possible, manually. One patient was studied with the apparatus described by Rigler

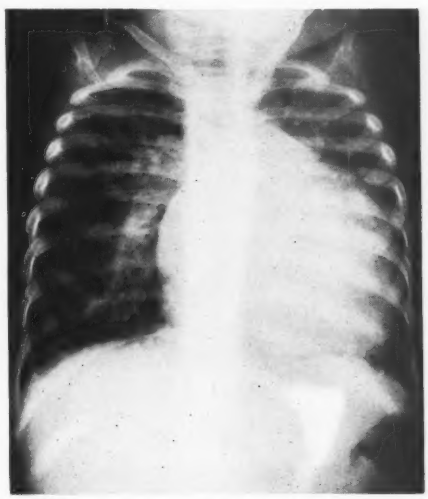

FIG. 9. Another patient demonstrating "box-like" shape.

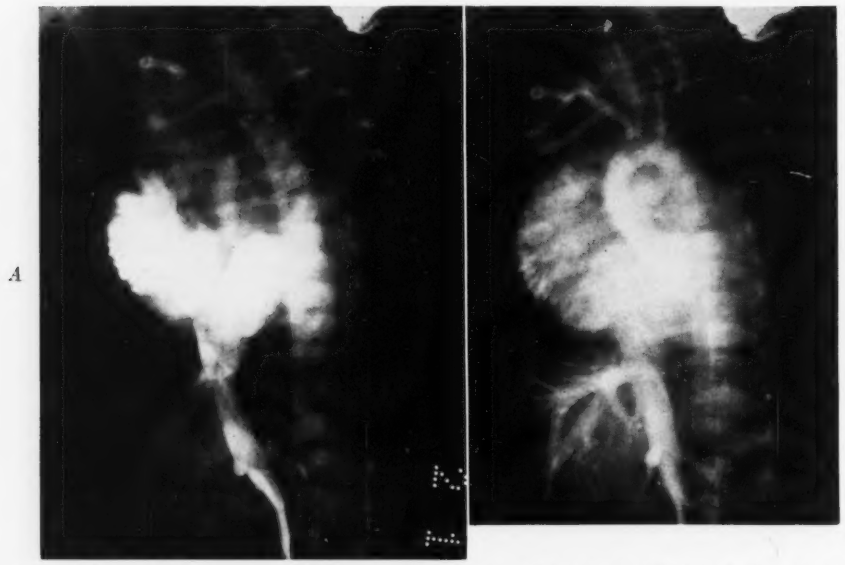

FIG. 10. *A* and *B*. Angiocardiogram demonstrating large right atrium, right to left shunt into small left atrium, followed by simultaneous opacification of a large pulmonary artery from the right ventricle and a small aorta from the left ventricle.

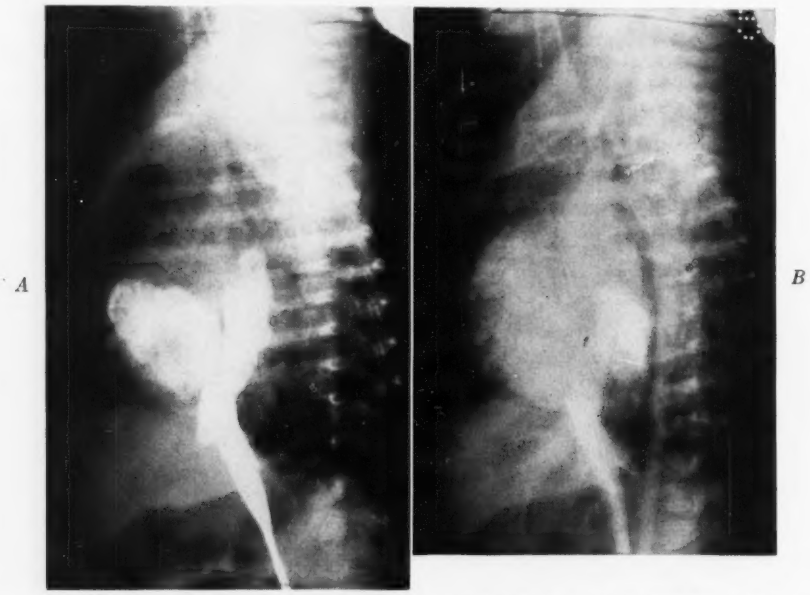

FIG. 11. *A* and *B*. Angiocardiogram demonstrating findings similar to figure 10.

and Watson[17] and the other two, with the Fairchild camera equipment.

In all, immediately following the opacification of a very large right atrium, one saw filling of the left atrium, and this cavity was quite small. Following this there was simultaneous opacification of the pulmonary artery, which was abnormally large, and of the aorta, which

was proportionately hypoplastic. The latter structure clearly filled from the left side of the heart and was seen with great clarity despite its small size. It filled well before it could have done so by circulation of the opaque material through the pulmonary circuit (figs. 10*A* and *B*, and 11*A* and *B*).

Yet another angiocardiographic sign is the dilution of the opaque material by the jet of nonopacified pulmonary venous blood entering the superior or inferior vena cava.

We feel, then, that there are several significant roentgen signs that can be perceived in this disorder. The so-called "figure of eight" appearance is probably pathognomonic of anomalous pulmonary drainage through "a persistent left superior vena cava" although some cases with this anomaly do not show the characteristic roentgen picture. The "box-like" shape of the heart, in association with increased pulmonary vascularity, while not an absolutely diagnostic sign, is highly suggestive of the anomaly in some of its forms. The angiocardiographic appearance described above appears to be typical of the disorder when evident.

Discussion

Total anomalous pulmonary venous return is a congenital malformation of serious significance that can be diagnosed during life if complete cardiac studies are available. The clinical picture of minimal cyanosis, a systolic murmur along the left sternal border and right axis deviation in the electrocardiogram should be suggestive clues. The x-ray findings are extremely helpful. The diagnosis is corroborated if the right atrial oxygen saturation equals or is higher than the peripheral arterial oxygen saturation.

Despite the potential curability of many of these lesions, surgery has been performed only rarely. There are 10 recorded attempts with two successful results in the literature.[2, 4, 16, 18, 19, 20] Six of our patients were submitted to surgery and three of these survived corrective procedures. It is planned to devote another paper to a more detailed account of the surgical management of this defect and also to discuss our suggestions for future surgical approaches.

A brief note on the operative material follows:

(1) R. F., a woman of 33, with a superior vena cava drainage had a successful anastomosis of the base of the left atrium to the side of the anomalous pulmonary vessel.

(2) D. H., a boy of 3 with a drainage into the right atrium, had a successful anastomosis of (1) the side of the left atrium to the side of the vein draining the left lung and (2) the tip of the left atrium to the cardiac end of the divided vein from the apical posterior segment of the left upper lobe.

(3) R. K., a 4 year old boy, survived a repositioning of the anterior portion of the atrial septum. It was moved to the right of the four pulmonary veins formerly entering directly into the right atrium. This is believed to be the first successful, completely corrective procedure performed for total anomalous pulmonary return.*

(4) M. M., a 3 month old boy with a "persistent left superior vena cava," died a few hours following a side-to-side anastomosis between the left atrium and the anomalous vessel.

(5) N. M., a 2 year old girl, died during an intracardiac procedure utilizing the atrial well. The drainage was thought to be into the right atrium but was actually into the coronary sinus.

(6) M. H., a 3 month old girl with coronary sinus drainage, died in the recovery room following a side-to-side anastomosis of the coronary sinus to the left atrium.

Currently we believe that the adoption of technics for totally bypassing the heart and lungs during the interval of surgical correction may improve the outlook of patients with this malformation.

Summary

1. Thirty cases of total anomalous pulmonary return are presented. Of these, 23 have been verified at autopsy, 3 at surgery and 4 additional cases are presumed to have this defect, after thorough clinical evaluation.

2. The anomalous pulmonary vessels may drain into any one of several systemic or visceral veins, but the most common drainage pathways are into a "persistent left superior vena cava," the coronary sinus or right atrium.

3. Patients with this defect show a mild

* This operation was performed by F. John Lewis and one of us (R. V.). We wish to thank Doctor Lewis for the privilege of mentioning this case.

cyanosis and a left sternal border, non-diagnostic, systolic murmur.

4. X-ray study may demonstrate the "figure of eight" or "box-like" shape with increased pulmonary vascularity; angiocardiograms may reveal a typical pattern of events.

5. The diagnosis is conclusive, if the right atrial oxygen saturation is equal to or higher than the peripheral arterial saturation.

6. Three of six patients submitted to surgery survived partial or totally corrective procedures.

Addendum

One infant, age 16 weeks and weighing 3.1 Kg., with total anomalous pulmonary venous drainage into the coronary sinus has undergone successful curative surgery utilizing the artificial oxygenator previously described from this clinic. A period of total cardiopulmonary bypass, lasting seventeen and one-half minutes, allowed the orifice of the coronary sinus to be anastomosed to the edges of the atrial septal defect from within the open right atrium.

Summario in Interlingua

1. Es presentate 30 casos de anormal retorno pulmonary total. De iste casos, 23 esseva verificate autopticamente e 3 chirurgicamente. In le remanente 4 casos le presentia del mentionate defecto es presumite super le base de caute evalutationes clinic.

2. Le anormal vaso pulmonary pote discargar se in un o altere de plure venas systemic o visceral, sed le plus commun vias de discarga es a in un "persistente vena cave sinistro-superior," le sinus coronari, o le atrium dextere.

3. Patientes con iste defecto exhibi leve grados de cyanosis e un non-diagnostic murmure systolic al margine sinistro-sternal.

4. Studios roentgenographic pote demonstrar un configuration simile al numero '8' o a un cassa con augmento de vascularitate pulmonar. Le angiocardiogramma pote revelar un configuration typic.

5. Le diagnose es conclusive si le saturation oxygenic del atrio dextere es equal o superior al saturation oxygenic del arterias peripheric.

6. Chirurgia correctional partial o total esseva interprendite in 6 casos. Tres de iste patientes superviveva.

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Observations on Angina Pectoris during Drug Treatment of Hypertension

By WALTER E. JUDSON, M.D., WILLIAM HOLLANDER, M.D. AND ROBERT W. WILKINS, M.D.

Antihypertensive drug treatment is capable of aggravating angina pectoris in hypertensive patients with coronary artery disease. The complication appears to be due to different hemodynamic mechanisms. Angina pectoris caused by hydralazine may result not only from a reduction in aortic perfusion pressure but also from increases in cardiac output and pulse rate which the drug produces. Coronary insufficiency, after the administration of hexamethonium, is usually associated with severe hypotension and results primarily from a reduction in aortic perfusion pressure. Hexamethonium was not found to prevent the anginal effects of hydralazine. Intravenous hydralazine is a sensitive test for coronary insufficiency but is not without untoward reactions.

IN recent years several potent blood-pressure-lowering drugs have become available for the treatment of arterial hypertension. Although extensive clinical trials with these hypotensive agents have proven their therapeutic effectiveness in reducing the level of blood pressure in certain hypertensive patients, some of them may produce adverse cardiovascular effects. In a long-term, careful study of a group of hypertensive patients, the oral administration of hydralazine (Apresoline) or ganglionic blocking agents (hexamethonium, pentolinium) was found occasionally to precipitate an attack of angina pectoris. In addition, an increased incidence of anginal complaints was observed during continuous chronic oral hydralazine therapy. The present study was undertaken, therefore, to determine the mechanisms by which such hypotensive agents might induce coronary insufficiency.[1]

PATIENTS AND METHODS

Seventeen patients, 7 males and 10 females, ranging in age from 40 to 65 years, with hypertensive cardiovascular disease and/or coronary artery disease were selected for the study. Regardless of the degree of abnormality of the resting electrocardiogram, all the patients were submitted to a modified "two-step" exercise tolerance test, which, in the absence of severe dyspnea or production of angina, required the arbitrary performance of 40 steps within three minutes. Of the 17 patients in the study, 11 had definitely abnormal electrocardiograms at rest. During the performance of the exercise tolerance test, 16 patients developed an abnormal pattern or further abnormalities of the electrocardiogram. In this group, only 13 patients complained simultaneously of anginal pain.

After 24 hours or more had elapsed, the patients were again studied before and after the administration of various hypotensive agents. An indwelling arterial needle was maintained in the brachial artery so that the arterial pressure could be measured continuously by a Sanborn electromanometer. Standard limb leads, I, II and III, and a single, unipolar precordial lead V_4, were recorded simultaneously with the arterial pressure, using a direct-writing Sanborn Poly-Viso. After the control measurements of blood pressure, pulse rate, and resting electrocardiogram had been obtained, hydralazine, hexamethonium or both, were given, usually intravenously. Simultaneous blood pressure measurements and serial electrocardiograms were recorded continuously after the administration of the drug for a period up to two hours.

RESULTS

Table 1 summarizes the effects of intravenous hydralazine. All 17 patients experienced chest pain, which, though not unlike their typical attacks of angina pectoris, was usually more severe and of longer duration. The pain began 5 to 18 minutes (average 12 minutes) after

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TABLE 1.—*The Effects of Apresoline in Patients with Coronary Artery Disease*

Patient, Age, Sex	Exercise Tolerance Test		Control Data			Dosage of Intravenous Apresoline, *mg.*	Effects of Intravenous Apresoline				Onset and Duration of Symptoms, *min.*	Comment
	Anginal pain	Abnormal ECG changes	Blood pressure, *mm. Hg*	Pulse rate, *Beats/min.*	ECG		Blood pressure *mm. Hg*	Pulse rate, *Beats/min.*	ECG	Symptoms		
F. H., 64, F	+	+	190/100	78	P.M.I. (old)	20	190/100	112	S-T decreased 1-4 mm. in I, II, V_4	Pressing substernal pain with radiation to left forearm	12, 60	B.P., P.R., and ECG changes occurred before symptoms. No relief with T.N.G.
J. S., 64, M	+	+	200/100	84	Normal	20	180/80	94	T flattened in I. S-T depressed 2 mm. in V_4	Tightness in lower retrosternal region	6, 34	No effect of carotid sinus stimulation on symptoms or ECG. T.N G. produced collapse with disappearance of angina
E. C., 62, F	+	+	200/90	96	L.V.H.	14	180/80	110	S-T depressed 1-2 mm. and T uprighted in I, II, V_4	Burning midsubsternal pain with aching of elbows	5, 24	No relief of symptoms with carotid sinus stimulation but with T.N.G. and inhalation of 100% O_2
W.F.,* 65, M	+	+	220/90	84	L.V.H.	20	180/60	100	T inverted and S-T depressed 1-5 mm. in I, II, V_4	Burning upper substernal pain	11, 120	Pain not relieved with T.N.G.
A. A.,* 40 M	+	+	180/100	70	L.V.H.	40	180/100	80	T uprighted in II and diphasic in V_4. S-T depressed 3 mm. in V_4	Burning pain in interscapular and mid retrosternal area	13, 40	ECG changes occurred before symptoms with slight increases in P.R. No relief with T.N.G.
R. B., 55, F	+	+	200/110	45	L.V.H. intermittent S.A. block	20	154/84	72	T diphasic in I and uprighted in III. S-T depressed 3 mm. in V_4	Tightness in upper retrosternum with radiation to left arm	17, 15	On next day 0.25 mg. intravenous Bellafoline doubled P.R. without causing chest pain or ECG changes
E. K.,* 63, F	−	+	280/160	80	Normal	20	230/100	90	T flattened in I, II, V_4. S-T depressed 2 mm. in V_4	Squeezing submanubrial pain with radiation to arm	9, >45	ECG not returned to normal for several hours
E. G., 57, F	+	+	160/60	72	Normal	20	120/40	90	T inverted in I, II	Pressing midsubsternal pain with radiation to left arm	10, 22	Changes in ECG and symptoms occurred at same time
I. R , 42, M	+	+	240/140	74	L.V.H.,	20	240/140	76	S-T depressed 2-3 mm. in I, II, V_4	Pressing submanubrial pain radiating down both arms	12, 15	—
P. E , 62, F	+	+	180/85	70	Normal	20	160/80	96	S-T depressed 1-2 mm. and T flat in I, II. V_4	Squeezing pain in interscapular and upper retrosternal region	21, 35	Changes in ECG and symptoms occurred at same time. No relief with inhalation of 100% O_2
L. A., 41, F	+	+	220/120	85	L.V.H.	40	80/50	110	T flat in I, II, V_4. S-T depressed 2 mm. in V_4	Aching midsternal pain	15, 90	No relief of pain with T.N.G. or inhalation of 100% O_2
L. F.,* 58, F	+	+	240/100	82	L.V.H.	17	205/80	106	S T depressed 1-2 mm. in I, II, V_4	Squeezing substernal pain	9, 20	Changes in ECG and P.R. occurred before symptoms
C. J., 50, M	+	+	160/90	88	M.D., A.F.	15	130/70	112	T inverted in I and uprighted in II. Freq. P.V.B.	Precordial burning pain	11, 25	No relief of pain with T.N.G.
H. H., 42, M	−	−	160/85	80	Normal	30	160/80	100	S-T depressed 1-2 mm. in I, II, V_4	Pressure in lower retrosternal area	9, 24	No relief of pain with carotid sinus stimulation
A. L., 42, F	−	+	170/80	72	M.D., R.B.B.	20	150/60	80	T uprighted in I, IV	Squeezing midsubsternal pain	16, 24	—
W. M., 48, M	+	+	120/70	86	M.D., P.V.B.	15	120/70	90	S-T depressed 2 mm. and T inverted in V_4	Left subcostal aching pain	18, 20	Pain occurred after ECG changes
G. C.,* 45, F	−	+	180/100	72	Normal	20	180/100	130	T flat and S-T depressed 1-3 mm in I, II, V_4	Severe crushing submanubrial pain with radiation down left arm	13 20	T.N.G. produced no relief of pain

P.M.I. = posterior myocardial infarction; L.V.H. = left ventricular hypertrophy; S.A. = sino-atrial; M.D. = myocardial damage; R.B.B. = right bundle branch block; A.F. = atrial fibrillation; P.V.B. = premature ventricular beat; T.N.G. = trinitroglycerine, sublingually.

* Patients who had received chronic oral Apresoline therapy and in whom angina appeared or increased in frequency and severity.

TABLE 2.—*The Effects of Apresoline in Patients with Angina Pectoris Pretreated with Hexamethonium*

Patients, Age, Sex	Procedure*	Blood Pressure, *mm. Hg*	Pulse Rate, *beats/min.*	ECG	Comments	Cardiac Index (Fick), *L./min./M²*
I. R., 42, M	Control	230/140	78	L.V.H.	—	
	C_6 (50 mg.)	180/110	82	No change	Dryness of mouth	
	Apresoline (50 mg.)	110/60	84	S-T depressed 2–3 mm. in I, II, and V_4	Pressing submanubrial pain radiating down both arms	
A. A., 41, M	Control	250/150	72	L.V.H.	—	
	C_6 (50 mg.)	160/110	76	No change	Dryness of mouth	
	Apresoline* (20 mg.)	130/80	76	T uprighted in II and inverted in V_4. S-T depressed 3 mm. in V_4	Stuffy nose, flushed "heaviness" in chest and interscapular region	
T. N., 52, F	Control	240/130	72	L.V.H.	—	
	C_6 (25 mg.)	180/100	80	No change	Dryness of mouth, blurring vision	
	Apresoline (20 mg.)	130/80	84	S-T depressed 1–4 mm. in I, II, V_4	Stuffy nose, squeezing substernal pain and aching of left elbow	
L. A., 41, F	Control	220/120	80	L.V.H.	—	3.79
	C_6 (6 mg.)	160/100	80	No change	Sleepy	3.76
	Apresoline (20 mg.)	120/75	82	T-wave uprighted in I, II, and V_4	Substernal pressure	4.35

* Intravenous Apresoline was given 8 to 29 minutes following pretreatment with hexamethonium.

exhibition of the drug and lasted 15 to 120 minutes (average 37 minutes). The administration of nitroglycerin or the inhalation of 100 per cent oxygen frequently failed to relieve the pain.

During the episode of chest pain the electrocardiogram showed noticeable changes in the T waves and depressions of the S-T segments. These electrocardiographic abnormalities were similar to those observed during an attack of angina induced by exercise. However, in contrast to intravenous hydralazine, exercise failed to produce angina pectoris in 4 of the 17 patients and to produce electrocardiographic changes in one of them.

The chest pain and electrocardiographic changes after intravenous hydralazine were usually associated with a reduction in the blood pressure and an increase in the heart rate. The average decrease in the systolic pressure was 27 mm. Hg and in the diastolic pressure, 18 mm. Hg, whereas the average increase in the pulse rate was 19 beats per minute. However, there were six patients who developed angina and abnormal changes in the electrocardiogram after hydralazine without appreciable decreases in blood pressure. Two of them also had no increase in pulse rate.

The effects of intravenous hydralazine in anginal patients pretreated with hexamethonium are summarized in table 2. In all four patients, three of whom had been previously studied with hydralazine alone (table 1), hexamethonium in doses of 6 to 50 mg. failed to prevent the development of angina pectoris or of electrocardiographic changes following intravenous hydralazine. Hexamethonium when given alone in these patients produced appreciable decreases in the blood pressure and slight changes in the pulse rate, but neither anginal pain nor change in the electrocardiogram. The administration of both drugs in combination was followed by very marked reductions in the blood pressure without marked increases in pulse rate. In one patient, L. A., in whom the cardiac output was measured (direct Fick), the

[illegible] ventricular beat; T.N.G. = trinitroglycerine, sublingually.
P V R = premature ventricular beat; T.N.G. = trinitroglycerine, sublingually.
* Patients who had received chronic oral Apresoline therapy and in whom angina appeared or increased in frequency and severity.

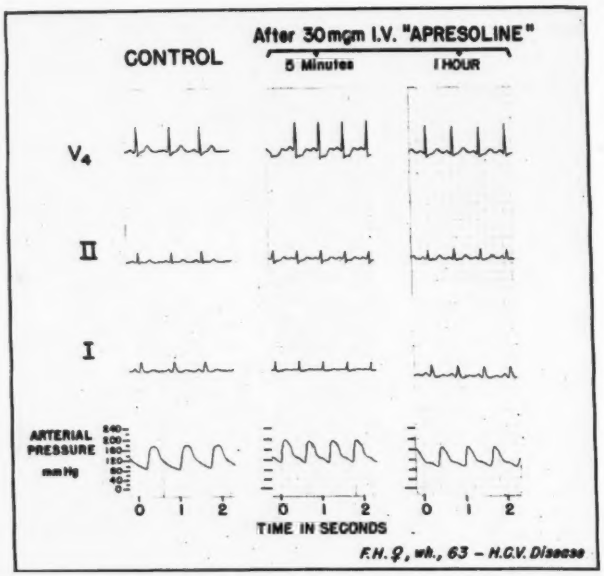

FIG. 1. Tracing showing the development of coronary insufficiency following intravenous hydralazine (Apresoline) without a change in blood pressure but an increase in pulse rate.

combination of drugs produced a slight increase in the cardiac output.

Illustrative Responses to Hydralazine and Hexamethonium

Figure 1 shows the typical ischemic pattern in the electrocardiogram after 30 mg. of intravenous hydralazine in a patient with hypertensive cardiovascular disease, old posterior myocardial infarction, and angina pectoris. Five minutes after the injection of the drug, the S-T segments in V_4 became depressed by 4 mm., in lead II, by 2 mm., in lead I, by 1 mm. without an associated change in the arterial pressure from the control levels, but with an appreciable increase in pulse rate (34 beats per minute). Seven minutes after the changes in the electrocardiogram had appeared, the patient had a typical attack of angina pectoris. One hour later the symptoms disappeared and the electrocardiogram reverted towards normal.

Figure 2 shows the effects of the oral administration of 50 mg. of hydralazine in a patient with hypertensive cardiovascular disease with angina pectoris. Thirty minutes after the drug, the S-T segment in V_4 had become depressed by 3 mm. without changes in the blood pressure and pulse rate. In this patient oral as well as intravenous hydralazine produced "ischemic" changes in the electrocardiogram but only after the intravenous administration did the patient develop chest pain.

Figure 3 shows the electrocardiographic changes and the blood pressure and pulse rate responses to the simultaneous administration of *l*-norepinephrine and hydralazine. This experiment was designed to determine whether the maintenance of the arterial pressure by norepinephrine would prevent the anginal effects of hydralazine. The initial infusion of *l*-norepinephrine alone caused an increase in the arterial pressure but did not produce evidence of coronary insufficiency. Five minutes after the intravenous administration of hydralazine, while the arterial pressure was maintained above its control levels by the continuous infusion of *l*-norepinephrine, severe anginal pain developed with marked "ischemic" changes in the electrocardiogram. The depressions in the S-T segments were associated with an increase in the pulse rate. From this experiment it appeared that a lowering of the aortic perfusion pressure

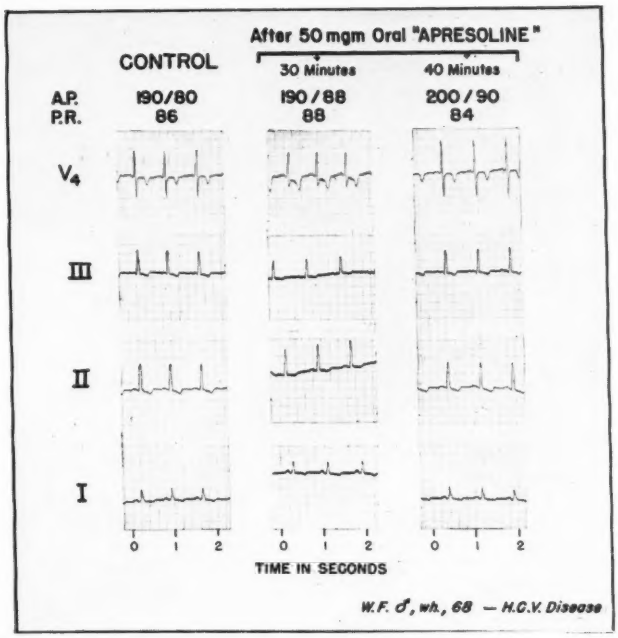

FIG. 2. Tracing showing abnormal changes in the electrocardiogram but no alterations in blood pressure or pulse rate after oral hydralazine (Apresoline) which was not associated with an attack of angina pectoris.

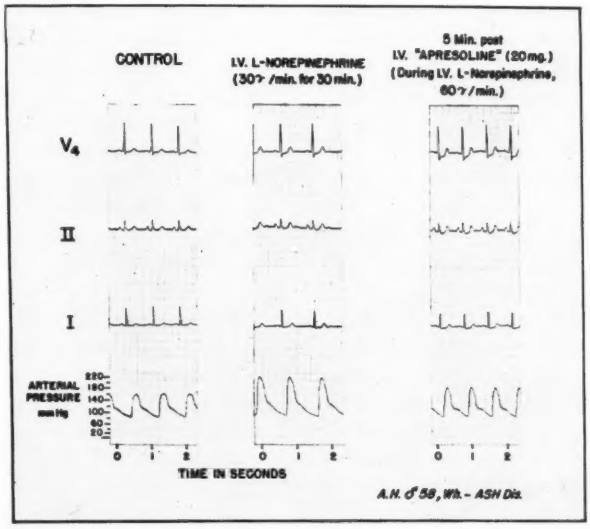

FIG. 3. Tracing showing that even though the arterial pressure was maintained by a continuous infusion of l-norepinephrine coronary insufficiency developed following intravenous hydralazine (Apresoline).

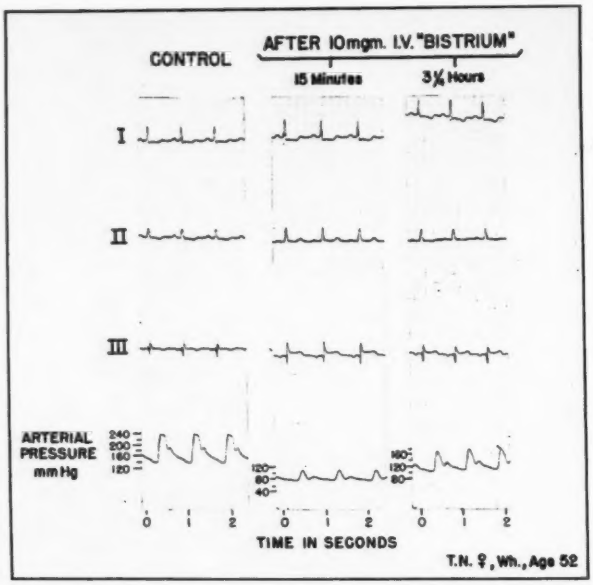

FIG. 4. Tracing showing "ischemic" changes in the electrocardiogram following intravenous hexamethonium (Bistrium) which was associated with a striking reduction in the arterial pressure.

of the coronary arteries was not the essential factor in the production of "coronary insufficiency" after hydralazine, but that the main factor was an increase in cardiac output associated with an increase in pulse rate.

Figure 4 shows a coronary insufficiency pattern in the electrocardiogram during severe and prolonged hypotension after intravenous hexamethonium in a patient with hypertensive cardiovascular disease. After the slow intravenous injection of 10 mg. of hexamethonium, the blood pressure fell precipitously with the patient becoming semicomatose. Although the patient had no chest pain during the severe hypotensive episode, the reciprocal changes in the S-T segments in leads I and III suggested coronary insufficiency. The blood pressure then rose, but the electrocardiographic changes persisted and a clinical course suggesting myocardial infarction (posterior wall) developed. In the presence of coronary artery disease, profound hypotension undoubtedly enhanced the coronary insufficiency and produced myocardial infarction.

Figure 5 shows an experiment designed to determine the importance of the level of blood pressure in producing coronary insufficiency after hexamethonium. Following the administration of a large dose of hexamethonium, no change occurred in either the arterial pressure or the electrocardiogram in the supine position. However, when the patient was tilted to the upright position, a profound fall in the blood pressure occurred, accompanied by angina pectoris and "ischemic" changes in the electrocardiogram. Following infusion of *l*-norepinephrine, there was a return of the blood pressure, but not to control levels, while the chest pain disappeared and the electrocardiogram returned to the upright control pattern. It is rather likely that even in a patient with coronary artery disease a moderate reduction in blood pressure, per se, after hexamethonium might fail to produce coronary insufficiency whereas a critical reduction could cause this complication.

Figure 6 is a tracing of one of four patients who developed angina pectoris after intravenous hydralazine though pretreated with hexamethonium. The control blood pressure was 220/120, pulse rate, 80 beats per minute, and the electrocardiogram showed a pattern of left

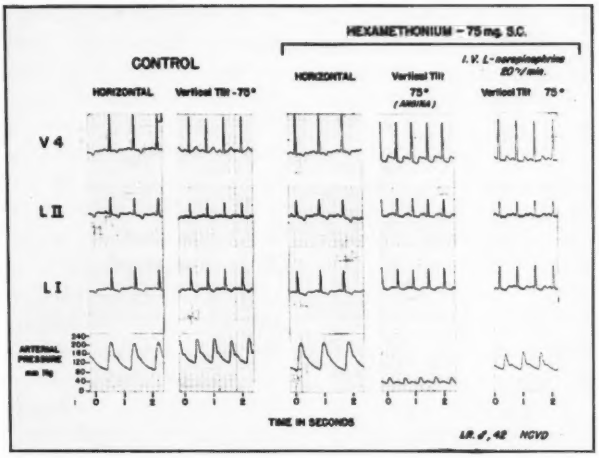

FIG. 5. Tracing showing adverse electrocardiographic changes and the development of angina pectoris after hexamethonium which was related to a critical reduction in the blood pressure.

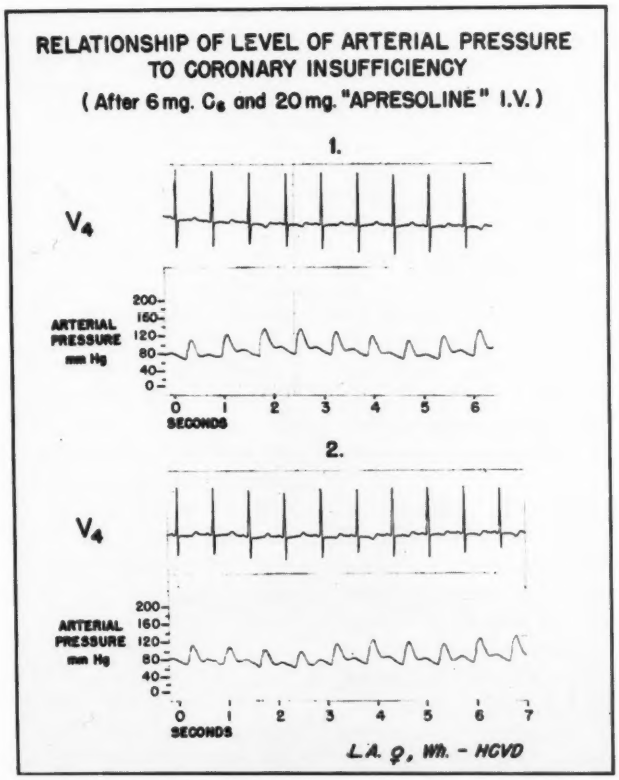

FIG. 6. Tracing showing the failure of hexamethonium (C_6) to prevent coronary insufficiency following intravenous hydralazine (Apresoline). The changes in the electrocardiogram were related to critical alterations in the blood pressure.

ventricular hypertrophy with inversion of T waves in leads I, II and V_4. Following the administration of hexamethonium, no changes in the electrocardiogram occurred. Twenty-nine minutes later hydralazine was given intravenously and produced further and striking reductions in the arterial pressure without a change in the pulse rate. The cardiac output at this time increased slightly (table 2). With these alterations the patient developed angina pectoris with uprighting of the T waves in leads I, II, and V_4. When the diastolic blood pressure was below 70 mm. Hg, the T wave in V_4 became upright but when it was above this level it again became inverted. Although hexamethonium partially blocked the pulse-rate-stimulating effect of hydralazine on the heart, the resulting drop in the blood pressure produced by the combination of the drugs probably became so critical that coronary blood flow decreased, precipitating coronary insufficiency and angina pectoris.

Discussion

In the clinical treatment of arterial hypertension, oral hydralazine frequently aggravates angina pectoris. In addition, this hypotensive agent may induce an attack of angina pectoris in patients with previously unrecognized coronary artery disease. Hydralazine is more apt to produce angina pectoris when administered intravenously, as is attested by the fact that all patients in this study had an attack which was usually severe and long in duration after the drug. In fact, the drug produced angina more regularly than the standard exercise tolerance test employed.

Although the complication of angina pectoris, following the administration of hydralazine, is usually associated with a reduction in the aortic perfusion pressure and an increase in the pulse rate, it apparently does not necessarily depend on these alterations. An increase in cardiac output produced by the drug may also be an important factor which operates to precipitate coronary insufficiency. In patients who develop angina pectoris without a change in the blood pressure and pulse rate, the increase in cardiac output and work of the heart may account for the coronary insufficiency. Although intravenous hydralazine has been reported to increase the coronary blood flow and the available oxygen per unit of left ventricular work in patients with essential hypertension,[2] it probably does not produce these changes in patients with coronary artery disease who have relatively fixed coronary vascular systems.

There are suggestions in the literature that hexamethonium may block the angina-producing effect of hydralazine.[3] However, no evidence was obtained in the present study to suggest that this might be the case. Even though hexamethonium may block the cardiac output and pulse rate responses to hydralazine, the resulting fall in blood pressure produced by this drug in combination with hydralazine may be so critical that coronary insufficiency is precipitated.

Ganglionic blocking agents (hexamethonium and pentolinium) occasionally produce angina pectoris in patients with coronary artery disease. However, this complication has never been observed by us without a lowering of the blood pressure. Therefore it appears that a reduction in blood pressure is the main hemodynamic factor that accounts for angina pectoris in patients receiving ganglionic blocking drugs. The importance of the aortic perfusion pressure has been illustrated in figures 4 and 5. It also has been clinically demonstrated, when postural hypotension causes angina which is relieved by lying down.

Coronary insufficiency occurring during treatment with other hypotensive agents such as veratrum, nitrites, dihydroergocornine, sodium azide or barbiturates is relatively rare. It appears that a very marked decrease in the blood pressure and the presence of sclerotic coronary arteries are required for the development of coronary insufficiency with hypotensive drugs.

Conclusions

(1) The data suggest that coronary insufficiency occurring in hypertensive patients with coronary artery disease during treatment with different hypotensive drugs may result from several different hemodynamic mechanisms.

(2) Coronary insufficiency (angina) after the administration of hydralazine does not result

solely from a reduction in the aortic perfusion pressure but also from increases in cardiac output and pulse rate.

(3) Coronary insufficiency after the administration of hexamethonium, on the other hand, results primarily from a reduction in the aortic perfusion pressure during the severe hypotension (especially postural hypotension) which this drug produces.

(4) Hexamethonium was found not to block the anginal effects of hydralazine.

(5) Intravenous hydralazine is a powerful agent capable of inducing subjective and objective evidence of coronary insufficiency. However, the severity and duration of the reactions to this drug appear likely to preclude its general clinical use as a test for coronary artery disease.

SUMMARIO IN INTERLINGUA

Pharmacotherapia antihypertensive es capace a aggravar angina de pectore in patientes con morbo de arteria coronari. Il pare que le complication es debite a differente mechanismos hemodynamic. Angina de pectore causate per hydralazina pote resultar non solmente ab un reduction del pression perfusional aortic sed etiam ab augmentos del volumine cardiac e del frequentia pulsari producite per le droga. Insufficientia coronari occurrente post le administration de hexamethonium es usualmete associate con sever hypotension e resulta principalmente ab un reduction del pression perfusional aortic. Nos non trovava que hexamethonium preveni le effectos anginal de hydralazina. Hydralazina intravenose es un sensibile test por insufficienta coronari, sed illo non es libere de reactiones negative.

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The Spatial Ventricular Gradient: Intermittent Wolff-Parkinson-White Syndrome, Intermittent Left Bundle Branch Block and Ventricular Premature Contractions

By MORDECAI A. BERKUN, M.D., RUSSELL H. KESSELMAN, M.D., EPHRAIM DONOSO, M.D. AND ARTHUR GRISHMAN, M.D.

Criteria are given for testing the ventricular gradient concept. The spatial ventricular gradient is then determined in three types of intraventricular conduction disturbances using the cube system of orthogonal bipolar leads. Correction of the isoelectric baseline for the effect of T_P on the QRS and T areas is made. The spatial ventricular gradient remains essentially constant both in magnitude and direction in intermittent Wolff-Parkinson-White syndrome and intermittent left bundle branch block despite marked changes in body surface electrocardiograms. Ventricular premature contractions produce marked deviations in the spatial ventricular gradient. The spatial ventricular gradient merits further study as one of the fundamental quantities in electrocardiography.

IN 1921, F. N. Wilson found a relationship between the forms of the QRS and T complexes in electrocardiographic curves.[1] He noted that changes in the QRS may be accompanied by corresponding changes in T of opposite sign. He concluded that the form of T depends on the order in which the various regions of the ventricles complete their electric activity. Changes in the duration of the electric response of particular regions of the ventricles, as seen with digitalis, tachycardia, exertion, and myocardial ischemia, were defined as primary T changes. On the other hand, changes in T accompanying changes in QRS, as in bundle branch block, were defined as secondary T changes.[2, 3] In 1931, Wilson introduced the term ventricular gradient for a vector defined by the electrical axis and the manifest area of QRST.[4]

The mean electric axis of QRS gives the mean direction in which the excitatory process spreads over the ventricles. Since recovery produces electric forces opposite in polarity to those produced by excitation, the mean electric axis of T must give the inverse of the mean direction in which the recovery process spreads over the ventricles. The ventricular gradient, which is the vector sum of the mean QRS and T vectors, therefore, represents the magnitude and direction of the electrical forces resulting from the lack of uniformity in the duration of the excited state in different portions of the ventricles. It points from the region in which the average duration of electrical systole is greatest toward the region in which it is least.[4, 5] The ventricular gradient concept neglects the effect of ventricular contraction upon the position and orientation of component cardiac muscle units with respect to each other and to the leads employed.[4]

Wilson limited his measurements to the frontal plane, using the areas of QRS and T in any two of the standard limb leads. S-T displacements were considered part of the recovery process except when due to injury currents.[3]

The most important applications of the frontal plane ventricular gradient to clinical electrocardiography were made by Ashman, Byer, Gardberg and associates.[6-10] They believed that an increase in stroke volume causes an increase in the magnitude of the frontal

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plane ventricular gradient, while an increase in heart rate or the use of digitalis[11] causes a decrease.

Ashman mentioned that the ventricular gradient might result from intramyocardial pressure differences,[12] while Lepeschkin felt that intramyocardial temperature variations were more important.[13]

Ashman never actually measured the spatial ventricular gradient although he devised a method of determining its direction in space.[10] Burch and his coworkers determined the spatial ventricular gradient, using leads I,V_F and V_B in a group of normal women during pregnancy and after delivery.[14] Jouve and associates determined the directions of the three-plane projections of the spatial ventricular gradient, using their lead system.[15] Ivancic and Mikulicic, using a different system of orthogonal bipolar leads, calculated the magnitude and direction of the spatial ventricular gradient in 100 normal subjects.[16] Simonson, Schmitt and co-workers were the first to report on the use of an electronic integrating circuit to obtain the spatial ventricular gradient.[17]

Objectives of this Investigation

Several authors have attempted to test the validity of the ventricular gradient concept in induced and spontaneous intermittent or transient intraventricular conduction disturbances, using frontal plane leads alone and the spatial ventricular gradient was not determined.

Wilson and his co-workers produced right bundle branch block in a dog and then caused varying fusion complexes by artificial stimulation of a single right ventricular focus. The frontal plane ventricular gradient showed a relatively small average variation.[4] Wilson also found fair agreement between the normal and aberrant ventricular conduction when he measured the frontal plane ventricular gradient in one patient with intermittent left bundle branch block.[3] Eckey and Schäfer subtracted the normal complexes in leads I, II and III from the abnormal complexes of intermittent Wolff-Parkinson-White syndrome in one case and obtained diphasic curves having approximately equal positive and negative areas.[18] They did not, however, discuss their findings in terms of the ventricular gradient concept. Fowler and Westcott reported six examples of right bundle branch block induced by cardiac catheterization and determined the frontal plane ventricular gradient before, during, and after the block.[19] Simonson and associates also studied one case with right bundle branch block and idioventricular rhythm in which the frontal plane ventricular gradient did not change appreciably.[17] Segers and Boyadjian calculated the frontal plane ventricular gradient in intermittent right and left bundle branch block and concluded that determination of the ventricular gradient projection on another plane was desirable.[20]

We have given consideration to the criteria for an ideal, and consequently crucial, test for the ventricular gradient concept in human beings. They are listed as follows:

(1) The spatial ventricular gradient is measured before or after a spontaneous or induced intermittent or transient intraventricular conduction disturbance and during the abnormal conduction.

(2) The measurements are made within a few seconds before and after the change in conduction to minimize the effect of alterations in other physiologic variables.

(3) Three noncollinear component leads are obtained simultaneously.

(4) The electrocardiographic tracings used are technically correct with minimum baseline wander.

(5) A variety of types of intraventricular conduction disturbances is studied.

(6) Correction is made for the effect of T_p on the baseline for the measurement of QRS and T areas.

(7) The cardiac rate remains essentially unchanged throughout the determinations.

(8) Marked tachycardia sufficient to cause overlapping of P and the preceding T is absent because it would then be impossible to construct any isoelectric baseline.

(9) The electrocardiographic records are obtained during the same phase of respiration to eliminate the effects of changes in cardiac position on the direction of the spatial ventricular gradient.

The studies to be described satisfy these criteria with the few exceptions to be noted.

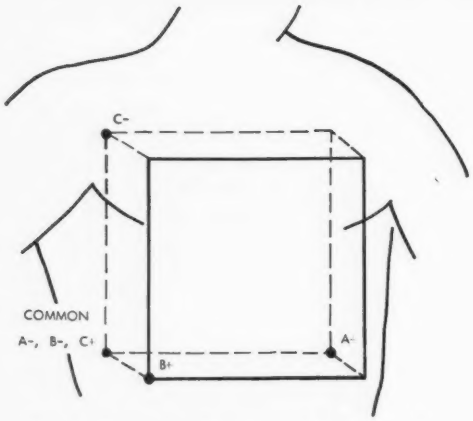

FIG. 1. Electrode placement and polarity of component leads A, B and C. (1) The common electrode (A−, B−, C+) is placed in the right posterior axillary line at the level of the first or second lumbar vertebra. (2) Electrode (A+) is placed in the left posterior axillary line at the same level as the common electrode. (3) Electrode (B+) is placed in the right anterior axillary line at the same level as the common electrode. (4) Electrode (C−) is placed in the right posterior axillary line over the right scapula.

The component leads used are the A, B, and C leads previously described.[21] They make up an orthogonal lead system presenting right-left, posterior-anterior, and superior-inferior components. The electrodes are placed approximately equidistant from the electrical center of the heart (fig. 1). The sphere is an ideal geometric figure for the vectorial study of an electric field. This is true because the lines connecting points equal distances along the surface of a sphere with the center of the sphere subtend equal angles and, therefore, indicate comparable quantities of the electric field in each lead. The eight corners of a cube represent eight equally distant points on a sphere's surface. Each electrode is sufficiently distant from the heart in the cube arrangement for the exploration of its field. The interposed tissue between the heart and the four electrodes is predominantly lung tissue. With the cube arrangement there is close correlation of the horizontal plane projection of the spatial vectorcardiographic loop and the chest leads

TABLE 1.—*Clinical Material*

Case No.	Initials	Age	Sex	Clinical Heart Disease	Types of Intraventricular Conduction
1	P. C.	59	F	Arteriosclerotic	Normal, Wolff-Parkinson-White
2	J. C.	20	M	Congenital (coarctation of the aorta)	Normal, Wolff-Parkinson-White
3	A. K.	37	M	None	Normal, Wolff-Parkinson-White
4	A. E.	67	F	Arteriosclerotic	Normal, Wolff-Parkinson-White, left bundle branch block
5	F. R.	62	F	Arteriosclerotic	Normal, left bundle branch block
6	W. P.	47	M	Hypertensive	Normal, left bundle branch block
7	D. D.	72	F	Arteriosclerotic	Normal, left bundle branch block
8	M. L.	45	F	Arteriosclerotic	Normal, incomplete and complete left bundle branch block
9	P. H.	54	F	Hypertensive	Normal, left bundle branch block
10	S. K.	53	M	Arteriosclerotic	Left bundle branch block, ventricular premature contractions from two foci
11	G. C.	59	M	Arteriosclerotic	Normal, ventricular premature contraction
12	C. R.	37	M	None	Normal, ventricular premature contraction
13	I. B.	84	M	Arteriosclerotic	Right bundle branch block, ventricular premature contraction, atrial fibrillation
14	M. V.	45	M	Rheumatic	Normal, ventricular premature contraction
15	I. G.	64	M	Arteriosclerotic	Left bundle branch block, ventricular premature contraction
16	G. P.	54	M	Aortic aneurysm	Normal, ventricular premature contraction
17	F. B.	41	F	Congenital	Normal, ventricular premature contraction

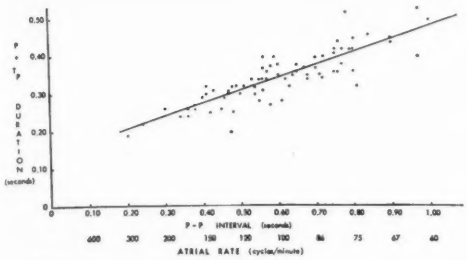

FIG. 2. The duration of atrial electrical activity ($P + T_P$) and its relationship to the P-P interval and the atrial rate.

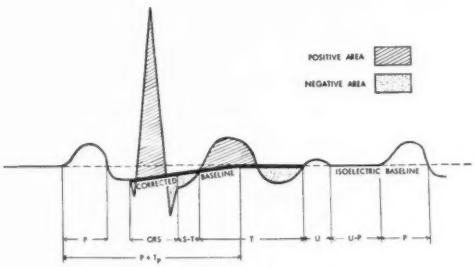

FIG. 3. Method of measuring areas.

recorded at the level of the dipole center of the heart.

The magnitude of the spatial ventricular gradient and its projections on any plane are usually expressed in microvolt-seconds (μ vs.), or in Ashman units (A.U.), each of which equals 4μ vs.[22]

MATERIALS AND METHODS

The records of 17 patients from the files of the Vectorcardiographic Laboratory of The Mount Sinai Hospital were suitable for this study (table 1).

All of the electrocardiograms were taken with the patient supine and with respiration temporarily held. A three-channel, direct-writing Technicon Cardiograph was used for all the records, and the determinations were made from simultaneous leads. Each patient had a standard 12-lead electrocardiogram and then simultaneous A, B and C leads were obtained. In most of the records the paper speed was 50 mm. per second. The standardization was adjusted so that a 1 mv. input gave a 15 mm. upright deflection. Occasionally, it was necessary to apply appropriate corrections for slight standardization differences.

The A, B and C component leads were then projected by means of an opaque projector against a wall resulting in a magnification of 8.1 diameters. The projected curves were traced along their upper margins and the time of onset of QRS, end of QRS and end of T were marked in the simultaneous leads using the most clearly outlined and usually the longest intervals for timing purposes. The U-P segment was taken as the true isoelectric baseline, and, where this was clearly identifiable, a straight line was drawn from the U-P segment preceding the cycle used to the U-P segment immediately following it. Where no clear U-P segment was found, or the baseline wandered appreciably, a line drawn from the start of P to the end of T (or U, if present), was used as the isoelectric baseline. In a few instances baseline wander was in more than one direction during a single beat so that any baseline constructed was subject to considerable error.

One of the difficulties encountered in any direct measurement of QRS and T areas is the magnitude

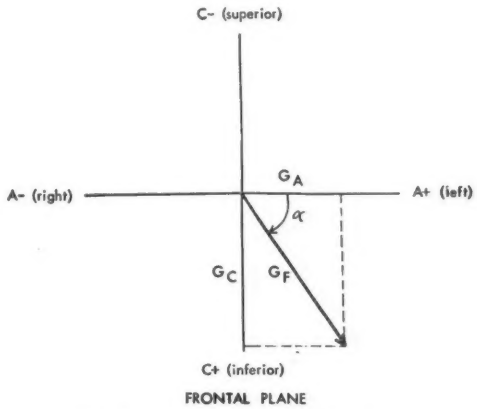

FIG. 4. Definitions of G_F and angle α.

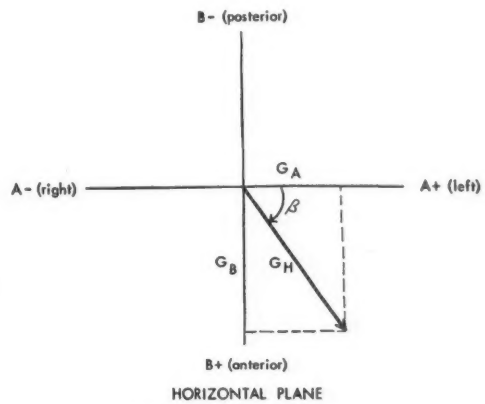

FIG. 5. Definitions of G_H and angle β.

TABLE 2.—*Results*

Case No.	Atrial Rate	Derived P + T_P (seconds)	Ventricular Conduction	A			B			C			G A.U.	G_P A.U.	α Degrees	G_H A.U.	β Degrees
				QRS A.U.	T A.U.	G_A A.U.	QRS A.U.	T A.U.	G_B A.U.	QRS A.U.	T A.U.	G_C A.U.					
1	65	0.47	Normal	+7.0	+3.3	+10.3	+0.5	+6.0	+5.5	+0.8	+6.3	+7.1	13.6	12.5	+35	11.6	+28
			WPW	−2.7	+11.5	+8.8	+10.2	−6.5	+3.7	+4.0	+4.1	+8.1	12.5	11.9	+44	9.2	+24
2	75	0.42	Normal	+4.7	+8.4	+13.1	−3.6	+3.5	−0.1	+5.5	+6.4	+11.9	17.4	17.4	+41	13.1	−1
			WPW	+10.7	+0.9	+11.6	+1.5	−1.8	−0.3	−3.9	+16.6	+12.7	17.3	17.3	+48	12.1	−2
3	102	0.34	Normal	+3.9	+4.8	+8.7	+0.5	+2.1	+2.6	+4.8	−0.8	+4.0	10.0	9.6	+24	9.3	+17
			WPW	+11.6	−0.4	+11.2	−8.9	+4.5	−4.4	−5.9	+10.5	+4.6	13.0	12.1	+23	12.0	−22
4	75	0.42	Normal	+5.5	+2.5	+8.0	−0.5	+1.4	+0.9	+1.0	+2.9	+3.9	8.9	8.8	+26	8.0	+6
			WPW	+8.2	−1.9	+6.3	−2.9	+5.1	+2.2	−7.3	+11.9	+4.6	8.1	7.8	+36	6.7	+19
			LBBB	+12.3	−5.0	+7.3	−6.2	+9.7	+3.5	−0.8	+4.2	+3.4	8.8	8.0	+25	8.1	+25
5	76	0.42	Normal	+6.0	+1.0	+7.0	−5.9	+2.5	−3.4	−0.1	+1.6	+1.5	7.9	7.1	+12	7.7	−26
			LBBB	+15.3	−8.7	+6.6	−16.8	+13.0	−3.8	−1.0	+3.4	+2.4	7.9	7.1	+20	7.5	−28
6	56	0.53	Normal	+6.0	−1.7	+4.3	−8.1	+5.1	−3.0	+1.9	−0.9	+1.0	5.6	4.7	+13	5.3	−35
			LBBB	+10.8	−5.2	+5.6	−18.4	+18.6	+0.2	−6.7	+4.9	−1.8	5.7	5.7	−19	5.6	+3
7	72	0.44	Normal	+4.6	+2.7	+7.3	−5.0	+0.0	−5.0	−0.6	+1.4	+0.8	8.8	7.4	+6	8.8	−34
			LBBB	+7.4	−3.5	+3.9	−13.3	+9.8	−3.5	+0.1	+1.3	+1.4	5.4	4.1	+21	5.3	−42
8	75	0.42	Normal	+6.0	+3.1	+9.1	−4.8	+3.3	−1.5	+5.5	+1.9	+7.4	11.9	11.8	+39	9.2	−9
	100	0.34	Inc. LBBB	+5.4	+0.6	+6.0	−10.7	+7.7	−3.0	+1.1	+1.5	+2.6	7.2	6.5	+24	6.7	−26
	100	0.34	LBBB	+7.9	−1.2	+6.7	−12.7	+11.6	−1.1	+1.5	+2.1	+3.6	7.7	7.7	+28	6.8	−10
9	83	0.39	Normal	+6.4	+0.9	+7.3	−1.4	−0.6	−2.0	+7.3	+0.3	+7.6	10.7	10.6	+46	7.6	−15
			LBBB	+13.5	−5.7	+7.8	−6.9	+6.5	−0.4	+6.2	−0.1	+6.1	10.0	9.9	+38	7.8	−3
10	100	0.34	LBBB	+16.8	−18.4	−1.6	−16.2	+13.5	−2.7	−2.2	−0.2	−2.4	3.9	2.9	−125	3.1	−121
			VPC 1	−2.0	+2.4	+0.4	−7.0	+1.3	−5.7	−8.8	+7.7	−1.1	5.8	1.2	−69	5.7	−86
			VPC 2	−19.5	+18.2	−1.3	+20.9	−23.3	−2.4	−4.5	+0.7	−3.8	4.6	4.0	−109	2.6	−119
11	79	0.41	Normal	+2.8	−1.6	+1.2	−8.6	+14.8	+6.2	+0.6	−1.2	−0.6	6.3	1.4	−29	6.3	+79
			VPC	+2.3	−5.3	−3.0	+5.7	−6.1	−0.4	+15.0	−16.1	−1.1	3.2	3.2	−160	3.1	−171
12	72	0.43	Normal	+2.2	+4.0	+6.2	−1.2	+4.5	+3.3	+1.0	−0.3	+0.7	7.1	6.3	+7	7.1	+28
			VPC	+8.2	−4.6	+3.6	+0.4	−1.2	−0.8	+6.9	−8.2	−1.3	3.9	3.8	−12	3.7	−7
13	—	—	RBBB	−4.7	+2.1	−2.6	+7.0	−8.0	−1.0	−5.8	+4.0	−1.8	3.3	3.1	−155	2.7	−158
			VPC	+1.8	−2.5	−0.7	+1.7	+0.4	+2.1	+1.8	−1.9	−0.1	2.2	0.7	−171	2.2	+107
14	70	0.44	Normal	−2.2	+3.1	+0.9	+1.6	+2.2	+3.8	+2.7	−0.1	+2.6	4.7	2.8	+71	1.4	+76
			VPC	+14.3	−15.3	−1.0	+0.0	+10.0	+10.0	−7.9	+8.9	+1.0	10.0	3.9	+135	10.0	+96
15	72	0.44	LBBB	+34.2	−30.0	+4.2	−29.8	+29.9	+0.1	−12.4	+7.9	−4.5	6.1	6.1	−47	4.1	+3
			VPC	−0.6	+9.7	+9.1	+7.2	−14.0	−6.8	−17.5	+17.9	+0.4	11.5	9.0	+1	11.5	−36
16	100	0.34	Normal	+8.4	+2.9	+11.3	−4.7	−0.4	−5.1	+0.5	+0.1	+0.6	12.3	11.3	+3	12.3	−23
			VPC	−2.0	+12.2	+10.2	+4.2	−8.2	−4.0	+3.3	−5.2	−1.9	11.2	10.5	−11	11.0	−21
17	63	0.48	Normal	+1.2	−2.2	−1.0	+1.0	+1.6	+2.6	+0.4	+0.6	+1.0	3.0	1.4	+135	2.8	+111
			VPC	+4.0	+0.3	+4.3	−6.0	+9.3	+3.3	−11.1	+18.2	+7.1	8.9	8.3	+59	5.4	+37

of T_P (representing atrial recovery). T_P is directed opposite to P and its enclosed area is approximately equal to that of P.[23] When P is small or isoelectric, T_P causes no discernible deviation of the baseline and no correction is necessary. When P is large and positive, T_P depresses the baseline for QRS and T considerably (particularly evident on the magnified tracings), and a baseline correction must be introduced or the measured areas of QRS and T will both be too small. Where P is large and negative, T_P is large and positive, and an opposite correction must be made or the measured areas will be too large.

Ashman[7] used an implied partial correction of the baseline for T_P in ventricular gradient determinations. Lepeschkin[13] suggested the use of a straight line from the start of QRS to the end of U as the baseline and set the notch between T and U as the end of T.

We approached this problem in a more direct fashion. The duration of atrial electric systole ($P + T_P$) was determined from 74 electrocardiograms with complete or incomplete heart block and this was plotted against the P-P interval. It was found that the duration of atrial electric systole decreases as the atrial rate increases and that there is a linear relationship when the $P + T_P$ duration is plotted against the $P - P$ interval[24] (fig. 2).

The duration of $P + T_P$ for the atrial rates of each case was derived from the graph. This was measured off along the isoelectric baseline from the start of P. Then a line was drawn from the onset of QRS to this point and this corrected baseline was used to measure the areas of QRS and T (fig. 3).

The tracings were attached to a flat board and the areas of QRS and T were measured with a planimeter. Areas above the corrected baseline were considered positive and areas below were considered negative. Each tracing was measured twice and the results averaged and then converted into Ashman units. The magnitude of the spatial ventricular gradient and the magnitudes and directions of its frontal and horizontal plane projections were calculated.

A series of symbols is defined and they will be used throughout the remainder of this presentation as well as in our future publications. Scalar quantities appear in ordinary type. Vector quantities appear in bold face type. (Modern publications in physics and mathematics universally use ordinary type for scalars and bold face type for vectors).

$\mathbf{G}$ is the spatial ventricular gradient, G is the magnitude of $\mathbf{G}$, $\mathbf{G}_F$ is the frontal plane projection of $\mathbf{G}$, G_F is the magnitude of $\mathbf{G}_F$, $\mathbf{G}_H$ is the horizontal plane projection of $\mathbf{G}$, G_H is the magnitude of $\mathbf{G}_H$, G_A is the magnitude of the projection of $\mathbf{G}$ on the A axis, G_B is the magnitude of the projection of $\mathbf{G}$ on the B axis, and G_C is the magnitude of the projection of $\mathbf{G}$ on the C axis.

Angle α is the smaller angle between $\mathbf{G}_F$ and the positive A axis and angle β is the smaller angle between $\mathbf{G}_H$ and the positive A axis.

Angle α is given a positive sign if $\mathbf{G}_F$ is inferior, and a negative sign if $\mathbf{G}_F$ is superior to the A axis. Similarly, angle β is called positive if $\mathbf{G}_H$ is anterior and negative if $\mathbf{G}_H$ is posterior to the A axis.

From the Pythagorean Theorem

$$G = \sqrt{G_A^2 + G_B^2 + G_C^2} \tag{1}$$

In the frontal plane (fig. 4)

$$G_F = \sqrt{G_A^2 + G_C^2} \tag{2}$$

and

$$\sin \alpha = G_C/G_F. \tag{3}$$

In the horizontal plane (fig. 5)

$$G_H = \sqrt{G_A^2 + G_B^2} \tag{4}$$

and

$$\sin \beta = G_B/G_H. \tag{5}$$

TABLE 3.—*Calculated Variations in G, G_F and G_H and the Changes in Angles α and β for the Various Types of Conduction*

Conduction Disturbance	Case No.	v_G (%)	v_F (%)	v_H (%)	α (Degrees)	β (Degrees)
Wolff-Parkinson-White Syndrome	1	8	5	25	9	4
	2	1	1	8	8	1
	3	23	11	25	1	39
	4	9	23	18	10	13
	—	—	—	—	—	—
	Average	10	10	19	7	14
Left bundle branch block	4	1	10	19	1	6
	5	0	0	3	8	2
	6	2	19	6	32	38
	7	48	57	50	15	8
	8	24	58	1	15	17
	9	7	17	3	4	13
	—	—	—	—	—	—
	Average	14	25	14	13	14
Ventricular premature contraction	10	39	83	59	56	35
	10	16	32	18	16	2
	11	65	78	68	131	110
	12	58	49	63	19	35
	13	40	126	20	34	95
	14	72	33	151	64	20
	15	48	58	95	53	49
	16	9	7	11	14	2
	17	99	142	63	76	74
	—	—	—	—	—	—
	Average	55	74	59	51	47

Case 8 was included in these calculations and in this table only for the change in conduction from incomplete to complete left bundle branch block.

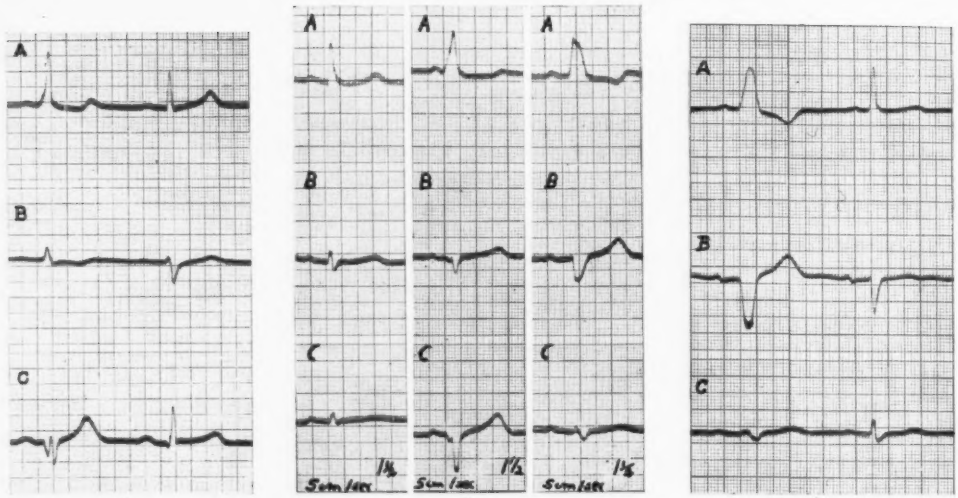

FIG. 6. Illustrative cases. *A*, Case 2, intermittent Wolff-Parkinson-White syndrome; *B*, case 4, normal conduction, Wolff-Parkinson-White syndrome and left bundle branch block; *C*, case 5, intermittent left bundle branch block.

RESULTS

The results are recorded in table 2. This contains the findings in four patients with intermittent Wolff-Parkinson-White syndrome, six patients with intermittent left bundle branch block, and eight patients with premature ventricular contractions.

For each case the table shows the atrial rate in cycles per minute, the derived P + T_p duration in seconds (from fig. 1), the types of intraventricular conduction, the magnitude of QRS and T areas, G_A, G_B, G_C, G, G_F, G_H, α and β. All magnitudes are in Ashman Units and all angles are in degrees.

Table 3 contains all the calculated variations in G, G_F, and G_H,* and the changes in angles α and β for the various types of conduction.†

Figure 6 contains representative A, B, and C component leads during control and abnormal ventricular conduction for cases 2, 4 and 5.

DISCUSSION

Four patients with intermittent Wolff-Parkinson-White syndrome were studied (cases 1, 2, 3 and 4). The average variation in G was 10 per cent (range 1 to 23 per cent); the average variation in G_F was 10 per cent (range 1 to 23 per cent); and the average variation in G_H was 19 per cent (range 8 per cent to 25 per cent). Angle α changed an average of 7 degrees (range 1 degree to 10 degrees), and angle β changed an average of 14 degrees (range 1 to 39 degrees). This is the first series of patients with intermittent Wolff-Parkinson-White syndrome in which $\mathbf{G}$, $\mathbf{G}_F$, and $\mathbf{G}_H$ have been determined. Within the limits of experimental error, $\mathbf{G}$, $\mathbf{G}_F$, and $\mathbf{G}_H$ did not change in magnitude or direction from that accompanying normal intraventricular conduction.

There were six patients with intermittent left bundle branch block (cases 4, 5, 6, 7, 8, and 9). The average variation in G was 14 per cent (range 0 to 48 per cent); the average variation in G_F was 25 per cent (range 0 to 58

* Let G be G_1 during control conduction, let G be G_2 during altered conduction, and let v_G be the per cent variation in G. Then

$$v_G = \frac{2\sqrt{(G_2 - G_1)^2}}{G_1 + G_2} \times 100\%$$

The symbols v_F and v_H are similarly defined for the per cent variation in G_F and G_H.

† The absolute values of the angle changes in degrees are used and these are indicated by the symbols $|\Delta\alpha|$ and $|\Delta\beta|$.

per cent); and the average variation in G_H was 14 per cent (1 to 50 per cent). There was an average change in angle α of 13 degrees (range 1 to 32 degrees), and in angle β of 14 (2 to 38 degrees). The changes in magnitude and direction of **G**, $\mathbf{G}_F$ and $\mathbf{G}_H$ are within the error of the determination and this indicates that **G** does not change in left bundle branch block. Unfortunately, our series did not contain any instances of intermittent right bundle branch block and we can give no confirmation of the ventricular gradient concept in that conduction disturbance, though we assume that it will be proved valid here, too.

Case 4 (see fig. 6), which showed normal conduction, Wolff-Parkinson-White conduction, and left bundle branch block is of particular interest not only because of the rarity of this combination but that the records were obtained at a single session and they can, therefore, be compared with each other. As can be seen from table 2 and figure 6, **G**, $\mathbf{G}_F$ and $\mathbf{G}_H$ were almost the same whereas the forms of the electrocardiographic complexes in the component leads were quite different from each other.

Eight cases with ventricular premature contractions were in the studied group (cases 10, 11, 12, 13, 14, 15, 16 and 17). The average variation in G was 55 per cent (range 9 to 72 per cent); the average variation in G_H was 74 per cent (range 7 to 142 per cent); and the average variation in G_H was 59 per cent (range 11 to 151 per cent). The change in angle α averaged 51 degrees (range 16 to 131 degrees), and in angle β averaged 47 degrees (range 2 to 110 degrees). These changes in **G**, $\mathbf{G}_F$ and $\mathbf{G}_H$ in ventricular premature contractions are about three to four times larger than the changes found in the same quantities in the cases with Wolff-Parkinson-White conduction and in the cases with left bundle branch block and are definitely outside the limits of observational error. **G**, therefore, changes both in magnitude and direction during ventricular premature contractions. Despite the divergent results obtained with ventricular premature contractions some positive correlation of lower magnitude appears to be present, but a much larger series of similarly studied patients would be required in order to reliably determine the degree of this correlation.

In the fifteen types of ventricular fusion complexes produced by Wilson and his associates in their dog experiment,[4] there was a 19 per cent average variation in G_F as determined from the Einthoven limb leads (range 4 to 46 per cent).* This experiment is not quite analogous to spontaneously occurring ventricular premature contractions in human hearts, some of them diseased. Burger and associates studied vectorcardiograms simultaneously obtained, using two different lead systems.[25] For normal conduction there was good correlation between the two vectorcardiograms, but for the ventricular premature contractions the correlation was poor. Their explanation was that the excitation spreads differently over the heart in the two types of conduction, and, because of the uneven distribution of insulating fatty tissue on the surface of or around the myocardium, the current field in the thorax is affected differently in normal and premature beats. Because of the abnormal pathway of the excitation wave in extrasystoles, the sequence of stimulation of different portions of the myocardium may vary greatly. This, in turn, may cause considerable shifts of the dipole center during the spread of the excitation wave accompanying an extrasystole which may affect the two lead systems used by Burger and his associates to a varying degree without having any additional significance. Another possibility is a basic difference between the excitatory and recovery processes in ventricular premature contractions as compared with normal conduction, Wolff-Parkinson-White conduction, and left bundle branch block. In ventricular premature contractions excitation takes place at differing times following the preceding beat and thus may occur during the relative refractory period or supranormal conduction phase of the ventricular muscle. Our findings strongly suggest that ventricular premature contractions are poorly suited to the investigation or confirmation of the ventricular gradient concept.

To compare **G** and $\mathbf{G}_F$ obtained by others,

* This calculation was made by us using Wilson's published data.[3]

using different lead systems, with our results obtained with the cube arrangement, it is necessary to relatively standardize the systems with respect to the actual electric field strength of the cardiac vector. To compare the cube with a system based on the Einthoven limb leads one may assume that the heart is immersed in a homogeneous volume conductor of infinite extent and that the lead electrodes are equidistant from the heart. Making the above assumptions, which are only approximations for any given subject, it has been calculated that the deflections in the standard limb leads of Einthoven have a 1.5 times greater amplitude than those in the cube system for the same magnitude of heart vector.[26] Consequently, to compare our values of G with those of Simonson and co-workers,[17] or our values of G_F with those of Ashman and his colleagues,[6-10] or others using the Einthoven limb leads, our gradient magnitudes must be multiplied by the factor 1.5. However, the lead system of Ivancic and Mikulicic[16] utilizes bipolar orthogonal leads and no standardization factor is required for comparison.

The consistency of the values of **G** both as to magnitude and direction in intermittent Wolff-Parkinson-White syndrome and intermittent left bundle branch block is indicative of the validity of the A, B, and C orthogonal lead system in electrocardiographic and vectorcardiographic practice.

Sources of Error

There are variations in the vertical thickness (along the voltage axis), of the electrocardiographic curve, depending on the shape of a deflection. This is due to incomplete burning of the heat-sensitive paper coating by the stylus at high speeds of deflection. The finite width of the stylus in the horizontal direction (along the time axis), affects the area under any curve if the rate of ascent is different from the rate of descent. By consistently making all tracings along the upper edge of the projected curves this error was kept to a minimum. In case 7, the upper edge of the original electrocardiograms was frequently poorly visible and the error in tracing the projected curves was probably large.

Baseline wander introduces an error of variable extent, particularly when the wander is in more than one direction. Case 13 had an irregular baseline due to atrial fibrillation.

The T_p correction is only an approximation for any individual record but the error introduced is probably relatively small.

Other minor errors resulted from 60 cycle per second alternating current electric interference, limitation of planimeter accuracy, and the human error in tracing the projected curves and using the planimeter.

Cases 7 and 8 were included in this study even though our criteria were not completely satisfied. In each, the intermittent left bundle branch block was produced by exercise. In case 7, the heart rate remained unchanged at 75 per minute, but in case 8, the heart rate increased from 75 per minute during normal conduction to 100 per minute during the two degrees of left bundle branch block. G, G_F and G_H decreased in both cases. Diminution of the ventricular gradient occurs with any increase in heart rate.[7] Case 7 is included in the calculations of average changes and all subsequent discussion of results, but in case 8 normal conduction is excluded and only the results in the two degrees of left bundle branch block are referred to in table 4 and subsequently. Case 8, as far as we know, is the first demonstration that G decreases on increase in heart rate, all previous conclusions being based on the observed decrease in G_F.

Conclusions

Our observations show that the spatial ventricular gradient can be readily determined, using the bipolar orthogonal component leads A, B and C of the cube system of vectorcardiography. The measurement of the spatial ventricular gradient is a significant addition to the understanding and also to the clinical analysis of the electric events of the cardiac cycle. The constancy of the magnitude and direction of the spatial ventricular gradient during normal intraventricular conduction, Wolff-Parkinson-White syndrome, and left bundle branch block emphasizes the value and significance of the gradient concept. When Wolff-Parkinson-White conduction or left

bundle branch block (and frequently left or right ventricular hypertrophy), are found in an electrocardiographic record, other changes due to myocardial damage or infarction are obscured. The spatial ventricular gradient may then be useful in diagnosis under these conditions by comparison with either a previous ventricular gradient determination made on an earlier record of the same patient or a set of normal standards.

It is apparent that the technics employed in this study are too time-consuming to be used in a very large series of cases. However, this project is a necessary preliminary to the automatic electronic recording of the spatial ventricular gradient.

Problems that we intend to investigate, using electronic apparatus and technics, are the determination of the range of the magnitude and the direction of the spatial ventricular gradient in normal individuals as well as similar measurements in ventricular hypertrophy, myocardial damage, myocardial infarction, and electrolyte disturbances, and the evaluation of the extent of digitalization.

Summary

(1) The spatial ventricular gradient and its projections on the frontal and horizontal planes are measured both in magnitude and direction, using an orthogonal cube lead system consisting of right-left, posterior-anterior and superior-inferior leads (A, B and C leads).

(2) A method of correcting for the effect of T_p on the areas of QRS and T is described.

(3) The spatial ventricular gradient is determined in four patients with intermittent Wolff-Parkinson-White syndrome during normal and abnormal intraventricular conduction. The spatial ventricular gradient did not change significantly in either magnitude or direction.

(4) The spatial ventricular gradient is determined in six cases with intermittent left bundle branch block and there are no significant changes in its magnitude or direction in the two types of conduction.

(5) The spatial ventricular gradient is measured in eight cases with ventricular premature contractions and there are significant changes both in magnitude and direction when compared with the control conduction. The results suggest that some positive correlation of lesser degree would be found if a larger series of cases is studied.

(6) A single case showing normal conduction, Wolff-Parkinson-White conduction and left bundle branch block is reported. There is no significant change in the magnitude or direction of the spatial ventricular gradient.

(7) In a single case, the spatial ventricular gradient is found to decrease in magnitude with an increase in heart rate.

(8) Criteria for testing Wilson's concept of the ventricular gradient are given and this concept is found to be valid.

(9) The results indicate that the orthogonal bipolar cube A, B and C lead system present reliable projections of the cardiac vector.

Summario in Interlingua

(1) Le spatial gradiente ventricular e su projectiones super le planos frontal e horizontal es mesurate in magnitude e direction per medio de un orthogone systema cubic de derivationes, consistente de derivationes dextero-sinistre, postero-anterior, e supero-inferior (A, B, e C).

(2) Es describite un methodo que rectifica le effecto de T_p super le areas de QRS e T.

(3) Le spatial gradiente ventricular es determinate in quatro patientes con intermittente syndrome Wolff-Parkinson-White durante normal e anormal conduction intraventricular. Le spatial gradiente ventricular non esseva significativemente alterate in o magnitude o direction.

(4) Le spatial gradiente ventricular es determinate in sex casos de intermittente bloco de branca sinistre. Il non ha significative alterationes in direction o magnitude del gradiente in le duo typos de conduction.

(5) Le spatial gradiente ventricular es mesurate in octo casos de prematur contractiones ventricular. Il occurre significative alterationes in e magnitude e direction in comparation con le conduction de controlo. Le resultatos rende probabile que un correlation positive de grados minus marcate esserea constatate si un plus extense serie de casos esseva studiate.

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The Tissue Catechol Amine Concentration of the Human Heart Determined by the Aluminum Hydroxide-Arsenomolybdic Acid Method

By J. M. B. Bloodworth, Jr., M.D. and E. von Haam, M.D.

With the aluminum hydroxide-arsenomolybdic acid method, which has recently been extensively modified in this laboratory, the tissue concentration of catechol amines was determined in 100 human hearts. The results were correlated with clinical history and autopsy findings. Previous work has suggested that cardiovascular disease and uremia were associated with an elevation in the heart catechol amine concentration, and that some cases of sudden death were associated with an elevated heart catechol amine concentration. In this study cardiovascular disease and uremia showed low or low normal values while not a single instance of sudden death could be explained by an abnormally elevated heart catechol amine concentration.

THE catechol amines, epinepihrine and norepinephrine, exert a wide range of pharmacologic effects. Norepinephrine is the chief sympathomimetic substance in mammals.[1] Under certain conditions of stress both hormones may be released from the adrenal medulla and other chromaffin tissue, with epinephrine representing approximately 80 per cent of the total.[2] Abnormally large quantities of catechol amines are found in the blood and urine of patients with a pheochromocytoma.[3, 4] In addition to their action on the muscle tone of blood vessels (blood pressure level) and cardiac rate, they increase body metabolism[5] and possibly stimulate the pituitary-adrenal axis.[6] Urine catechol amines are elevated in muscular work,[7] hypertension and myocardial infarction.[8-11] Both epinephrine and norepinephrine increase cardiac excitability[12, 13] and frequently cause depression or inversion of the T waves of the electrocardiogram.[14] Raab[15] has shown that injected epinephrine and norepinephrine are selectively concentrated in the myocardium.

Raab[16] has pointed out the possible toxicity resulting from the selective concentration of catechol amines in the myocardium and the increased metabolism (oxygen wasting effect) caused by these hormones. He postulates that they may reach a toxic level above which they can cause cardiac arrythmias and death. Raab[17, 18] has reported two, otherwise unexplained, sudden deaths in apparently healthy young adults. In both cases the tissue catechol amine concentration of the heart was elevated. In the hope that a large series of assays would shed light on this problem we have determined the tissue catechol amine concentration of 100 human hearts.

Materials and Methods

Hearts were obtained from the autopsy service of the Ohio State University Hospital and the coroner's service of Franklin County. Consecutive cases were obtained as far as possible. Embalmed hearts were not assayed because of the interference of formalin with the assay procedure. Occasional cases of acute myocardial infarction and severe valvular disease were saved for demonstration and thus excluded from the series.

The heart was obtained at autopsy (1 to 6 hours after death) and immediately quick-frozen (−50 C.). Assays were usually performed within 24 hours, never after more than two weeks. Fat and connective tissue were eliminated and several pieces of myocardium from different parts of both ventricles were weighed and extracted with trichloroacetic acid. The catechol amines were then concentrated on aluminum hydroxide and assayed with arsenomolybdic acid according to the method previously reported.[19]

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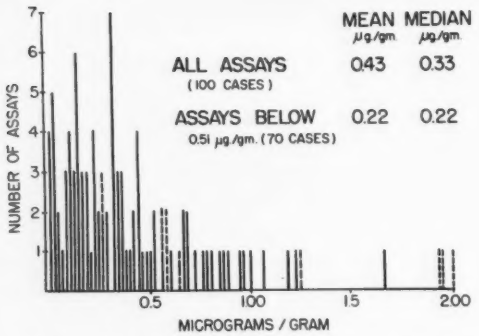

FIG. 1. The distribution of tissue catechol amine concentrations in 100 human hearts. The assay values from cases receiving catechol amines by injections are shown by a broken line.

RESULTS

The determination of the "normal" tissue catechol amine concentration of the human heart is complicated by several factors: (1) the value appears to vary in different mammalian species.[20-24] (2) One can rarely obtain hearts from "normal" human patients. (3) Most autopsy cases represent the result of several disease processes. We have, therefore, established our "normal" range by indirect methods. Figure 1 shows the distribution of all (100) human assays. The cases receiving injected catechol amines are shown by the dotted lines. In this diagram the normal values should group together and give a bell curve. The values below 0.50 μg. show this grouping. There are 70 cases in this group; both the mean and the median are 0.22 μg. per Gm. We were also able to obtain five hearts from apparently normal individuals who met instantaneous sudden death (cases 6, 13, 18, 22 and 83). The mean value for these five cases is 0.23 ± 0.16 μg. per Gm. With this data in mind we have arbitrarily established 0.25 ± 0.15 μg. per Gm. as the normal range. (The variation, 0.15 μg. per gram represents the estimated error of the over-all method).

As mentioned above almost all assays were done on patients suffering from several disease processes at the time of death. The mean value for the tissue catechol amine concentration of hearts associated with a given disease may be appreciably affected by other diseases present at the time of death. This effect can be eliminated statistically only by the accumulation of a large series of cases. We have, therefore, included (table 1) a short summary of each case for use in future correlation of data. In this table, the major clinical and pathologic diagnoses are listed with the immediate cause of death first. The blood pressure is recorded for all cases of hypertension, that is, above 150/90 mm. Hg. Occasionally there was a history of hypertension in coroner's cases, but no blood pressure recordings were available. Pertinent laboratory data and drug administration data are also included.

In seven cases (cases 12, 27, 38, 45, 53, 62 and 72) the patient was receiving intravenous norepinephrine at the time of death. All but one case showed an elevation of the assay value and the group gave a mean of 0.93 μg. per gram. One case (case 11) received 0.5 ml. of norepinephrine subcutaneously one-half hour before death without effect on the assay value.

In five cases (cases 34, 39, 61, 90 and 92) an attempt was made to inject intracardiac epinephrine after death. Two cases (cases 61 and 90) showed a marked elevation of the assay value. Apparently the needle did not reach the myocardium in the other three cases.

The seven cases receiving intravenous norepinephrine and the two cases receiving intracardiac epinephrine were not used in the compilation of mean values for various disease states.

DISCUSSION

The literature contains numerous papers dealing with the tissue catechol amine concentration of animal hearts.[20-24] The only multiple case studies of the tissue catechol amine concentration in human hearts are reported in the papers by Holtz, Kroneberg and Schumann[25]; Raab and Gigee,[26] and Raab.[27] Direct quantitative comparisons between the studies cannot be made because of the difference in assay technics. However, despite variation in technic and the impossibility of obtaining "pure" disease states, certain observations and comparisons are possible.

The nine cases receiving extraneous catechol

TABLE 1. *The Tissue Catechol Amine Concentration of the Human Heart*

ase No.	Race, Sex and Age	Clinical and Laboratory Data: Autopsy Findings	Heart Catechol Amine Content μg./Gm.
1	W/M/54	Pneumonia, insulin sensitive diabetes mellitus.	0.72
2	W/M/29	Delirium tremens (young adult).	0.35
3	W/M/74	Pneumonia, fibrosarcoma.	0.67
4	W/M/22	Death three hours after gun shot wounds of lungs and aorta. Pulmonary edema.	0.96
5	W/F/51	Shock, Laennec's cirrhosis, miliary tuberculosis.	0.44
6	W/F/63	Sudden death, head trauma with cerebral hemorrhage due to fall. Pulmonary congestion and edema.	0.22
7	W/F/26	Diabetes mellitus with glomerulosclerosis and Kimmelstiel-Wilson syndrome. Two months after total adrenalectomy. B.U.N. 86 mg.%. B. P. 190/100 mm. Hg.	0.53
8	W/F/17	Carbon monoxide poisoning, pulmonary congestion and edema.	0.80
9	W/M/59	Pneumonia, squamous carcinoma of lung, severe pulmonary edema.	0.45
10	C/F/36	Carcinoma of breast, carcinomatosis, ascites.	0.29
11	W/M/80	Pneumonia, postoperative shock, carcinoma of urinary bladder. 1 cc. of norepinephrine s.c. ½ hr. ante mortem.	0.27
12	W/F/62	Postoperative shock, pelvic inflammatory disease, pancreatitis norepinephrine i.v. B. P. 200/105 mm. Hg.	0.27
13	W/M/54	Sudden death from gun shot wound of heart. Ethanol intoxication.	0.36
14	W/M/48	Sudden death. Events preceding death unknown. Organizing pneumonia, severe arteriosclerotic heart disease, probable coronary occlusion.	0.33
15	W/M/24	Convulsion, apparently healthy medical student, pulmonary and cerebral edema.	0.44
16	C/F/14	Drowning.	0.25
17	W/M/52	Pneumonia, Hodgkin's disease. Cortisone 300 mg. daily last two months of life.	0.39
18	W/M/84	Sudden death, rupture of congenital aneurysm of Circle of Willis.	0.22
19	W/F/39	Uremia, carcinoma of cervix with obstruction of ureters, pulmonary edema, pyelonephritis. B.U.N. 171 mg.%. B. P. 200/100 mm. Hg.	0.11
20	W/M/45	Septicemia, aplastic anemia, intestinal hemorrhage.	1.07
21	W/M/56	Shock due to hemorrhage from carotid artery. Squamous carcinoma of gingiva, emaciation.	0.34
22	W/F/32	Sudden death due to trauma by auto. Ethanol intoxication.	0.19
23	W/M/70	Fracture of skull, 1 day after craniotomy, pulmonary congestion and edema. Active rheumatic heart disease.	0.11
24	W/F/24	Pneumonia, leukosarcoma, hemorrhagic diathesis.	0.51
25	W/F/16	Osteogenic sarcoma.	1.19
26	W/M/53	Subdural abscess, 6 days after craniotomy, shock. Laennec's cirrhosis, diabetes mellitus, pneumonia, history of hypertension.	0.85
27	W/M/84	Pneumonia, congestive heart failure, fracture of hip, arteriosclerotic heart disease. Norepinephrine i.v.	0.58
28	W/M/72	Carcinoma of urinary bladder, 10 days postoperative. Jaundice. B.U.N. 87 mg.%. Serum bilirubin 3.4 mg.%.	0.08
29	W/M/30	Trauma due to airplane crash. Asphyxia, pulmonary congestion and edema. Interval between crash and death uncertain.	0.66
30	C/M/56	Trauma, hit by auto. Multiple fractures, massive hemorrhage, 3 days after craniotomy.	0.03
31	W/M/8	Acute stem cell leukemia.	0.22
32	W/M/85	Congestive heart failure, arteriosclerotic heart disease.	0.28
33	W/F/70	Cerebral infarct, arteriosclerotic cardiovascular disease, diabetes mellitus. B. P. 170/50 mm. Hg.	0.88
34	W/M/52	Acute myocardial infarction, arteriosclerotic heart disease. Intracardiac epinephrine. B. P. 150/100 mm. Hg.	0.00
35	W/M/46	Hemorrhagic diathesis, acute myelogenous leukemia.	0.33
36	W/M/50	Peritonitis, perforation of peptic ulcer, "alcoholic."	0.02
37	W/F/75	Carcinoma of the lung. B.U.N. 93 mg.%.	1.01
38	W/F/74	Carcinoma of the stomach, 6 days after resection, pyelonephritis, liver insufficiency. B.U.N. 181 mg.%. Norepinephrine i.v.	1.95

TABLE 1.—*Continued*

		Clinical and Laboratory Data: Autopsy Findings	Heart Catechol Amine Content μg./Gm.
39	C/M/64	Carcinoma of the lung, 2 hours after resection, digitalized. Intracardiac epinephrine. B. P. 165/95 mm. Hg.	0.32
40	W/M/53	Sudden death, arteriosclerotic cardiovascular disease, "probable" acute myocardial infarct, pulmonary edema.	0.25
41	W/F/51	Hemorrhagic diathesis, acute monocytic leukemia.	0.12
42	W/M/38	Contusions of brain, ethanol intoxication. (DOA). Interval between injury and death uncertain.	0.14
43	W/F/38	Traumatic cerebral hemorrhage, fracture of skull, pulmonary congestion and edema. (DOA). Interval between injury and death uncertain.	0.37
44	W/M/48	Electrocution.	0.05
45	W/M/70	Gangrene of gallbladder, 19 days postoperative. Pulmonary congestion and edema. Lower nephron nephrosis. B.U.N. 84 mg.%. Norepinephrine i.v. B. P. 146/92 mm. Hg.	1.94
46	W/F/56	Hemorrhagic diathesis with pericardial tamponade, chronic myelogenous leukemia. B.U.N. 55 mg.%.	0.06
47	W/M/72	Hemorrhage from esophageal varices, Laennec's cirrhosis.	0.18
48	W/M/72	Acute pulmonary edema, carcinoma of the colon. B.U.N. 54 mg.%.	0.10
49	W/M/79	Carcinoma of the prostate, 3 days postresection, pulmonary congestion and edema.	0.00
50	W/M/85	Pneumonia, nodular hyperplasia of prostate with urethral obstruction, pyelonephritis. B.U.N. 67 mg.%.	0.16
51	W/F/41	Acute ethanol intoxication, pulmonary congestion and edema.	0.76
52	C/M/65	Pneumonia, cerebral infarct.	0.05
53	W/F/68	Peritonitis, peptic ulcer, 12 days after gastric resection. Norepinephrine i.v.	0.64
54	W/F/29	Asphyxia due to convulsion, idiopathic epilepsy. Cerebral edema. (DOA).	0.33
55	W/F/50	Pneumonia, rheumatic pancarditis, chronic polyarteritis, severe arteriolar nephrosclerosis.	0.95
56	C/F/4	Septicemia, acute lymphatic leukemia, multiple abscesses.	0.86
57	W/M/22	Head trauma, rupture of corpus callosum, 2 days after auto accident.	0.03
58	W/M/71	Pneumonia, giant cell carcinoma of thyroid, 9 days postoperative. Carcinoma metastatic to lung. Pulmonary infarcts.	0.22
59	W/F/70	Uremia, arteriolar nephrosclerosis. B.U.N. 98 mg.%. Five weeks after cerebral thrombosis.	0.14
60	W/M/43	Shock, hemorrhagic diathesis, chronic myelogenous leukemia.	0.68
61	W/F/41	Ventricular fibrillation, 4 days after hysterectomy for menorrhagia. B.U.N. 94 mg.%. Intracardiac epinephrine. B. P. 224/114 mm. Hg.	2.01
62	W/M/76	Peritonitis, carcinoma of colon. B.U.N. 81 mg.%. Norepinephrine i.v. Epinephrine i.m.	0.57
63	W/M/67	Uremia, prostatic hyperplasia with urethral obstruction. Laennec's cirrhosis. B.U.N. 109 mg.%.	0.09
64	W/M/38	Encephalitis, pneumonia. B.U.N. 58 mg.%.	0.42
65	W/M/74	Carcinoma of colon, 5 days after colostomy, pyonephrosis. B.U.N. 60 mg.%.	1.67
66	W/M/56	Peritonitis, perforation of duodenal ulcer, carcinoma of the lung, pneumonia.	0.09
67	W/M/45	Trauma with multiple fractures, 5 days after auto accident. Fat emboli to brain and kidneys. Pneumonia.	0.48
68	C/F/57	Hemoperitoneum, sarcoma botryoides, pulmonary edema. B.U.N. 50 mg.%.	0.11
69	C/F/62	Subdural hematoma (probably spontaneous), "alcoholic."	0.12
70	W/M/59	Cerebral hemorrhage. Tetraethyl ammonium chloride. B. P. 300/120 mm. Hg.	0.02
71	W/F/65	Pneumonia, carcinoma of breast, pleural effusion.	0.33
72	W/F/54	Peritonitis, postoperative shock. Two days after cholecystectomy for cholelithiasis. Norepinephrine i.v.	0.59
73	W/M/5	Intraperitoneal hemorrhage, 3 days after resection for intussusception, chronic myelogenous leukemia, cerebral edema.	0.17
74	W/M/42	Myocardial edema suggesting beriberi heart disease, "alcoholic."	0.21
75	C/M/38	Traumatic cerebral contusion and hemorrhage, 12 days after auto accident, pneumonia, pulmonary edema. B.U.N. 60 mg.%.	0.33

TABLE 1.—*Continued*

		Clinical and Laboratory Data: Autopsy Findings	Heart Catechol Amine Content μg./Gm.
76	W/M/55	Pneumonia, chronic myelogenous leukemia, hydronephrosis, lower nephron nephrosis. B.U.N. 132 mg.%.	0.14
77	W/M/4 mo.	Interstitial pneumonia, sudden death at home.	0.41
78	W/M/36	Acute myocardial infarction, severe arteriolar sclerosis suggests hypertension; history not available. (DOA).	0.13
79	W/F/1½	Hemorrhagic septicemia, probably meningococcal.	0.14
80	C/M/42	Uremia, nephrosclerosis, congestive heart failure. B.U.N. 166 mg.%. B. P. 220/150 mm. Hg.	0.01
81	W/M/69	Carcinoma of lung.	0.35
82	W/F/69	Pneumonia, congestive heart failure. History of giant follicular lymphoma, thyroidectomy. B.U.N. 114 mg.%. B. P. 190/100 mm. Hg.	0.00
83	C/F/32	Sudden traumatic death, hit by auto, ethanol intoxication.	0.15
84	W/F/67	Gastrointestinal hemorrhage, subacute duodenal ulcer.	0.18
85	W/F/6	Electrocution, adrenal hemorrhage.	0.78
86	W/M/80	Traumatic sudden death, hemothorax, fall, old myocardial infarcts, (interval between fall and death ½ hour).	0.47
87	W/M/23	Acidosis, diabetes mellitus, pyelonephritis. B.U.N. 50 mg.%.	0.56
88	W/F/31	Chronic myelogenous leukemia. Serum bilirubin 27 mg.%.	0.33
89	W/M/36	Chronic alcoholism, delirium tremens.	0.44
90	W/M/44	Acute pulmonary edema. Hypersensitivity reaction to nitrous oxide anesthesia. Intracardiac epinephrine.	1.24
91		Stillborn, premature.	0.68
92	W/F/50	Cardiac arrest, hernia repair, obesity. Intracardiac epinephrine. B. P. 150/100 mm. Hg.	0.37
93	W/M/73	Cerebral hemorrhage, diabetes mellitus.	0.14
94	W/M/66	Hemothorax, 1 day after resection for carcinoma of lung.	0.03
95	C/F/66	Pneumonia. B.U.N. 103 mg.%.	0.27
96	W/M/44	Hemorrhagic diathesis, acute monocytic leukemia, pulmonary congestion and edema.	0.17
97	W/F/28	Head trauma, 30 days after auto accident, pulmonary congestion.	0.43
98	W/F/27	Carcinoma of lung.	1.22
99	W/M/66	Peritonitis, infarct of intestine.	0.53
100	W/M/54	Myocardial infarcts, old and recent. Chronic pyelonephritis, carcinoma of prostate, carcinoma of kidney.	0.60

amines and showing a marked elevation in the assay value demonstrate the validity of the method. In view of the rapid degradation of injected epinephrine,[28] it has been suggested that true assay values can be obtained only from tissue which is removed during life and immediately frozen with liquid nitrogen or similar freezing technic. Our cases show that appreciable activity remains several hours after death and can be recovered if the tissue is simply frozen in the deep freeze within 2 to 6 hours after death. Unpublished data from this laboratory shows that tissue catechol amine degradation is quite slow until the tissue integrity is destroyed as by maceration in a Waring blender.

Although 21 cases (exclusive of those receiving catechol amines by injection) showed elevated values, no consistent change was produced by any disease state. Septicemia and other severe infections as well as sarcoma and diabetes mellitus showed a moderate elevation in the mean value. However, the number of cases in each group was small. Stress as a stimulus to catechol amine production or release has been considered. In this study, however, hemorrhagic shock, mechanical trauma and other conditions associated with severe stress did not produce a consistent elevation in the tissue catechol amine concentration of the human heart.

Heart Disease. Nineteen cases of heart disease

gave a mean tissue catechol amine concentration of 0.35 μg. per Gm. of heart muscle. If these cases are separated into disease entities there were 11 cases of hypertension with a mean value of 0.30 μg. per Gm.; five cases of congestive heart failure with a mean value of 0.16 μg. per Gm., and four cases of acute myocardial infarction with a mean value of 0.25 μg. per Gm. Thus the cases of heart disease whether taken as a group or divided into disease entities showed a preponderance of values well within or below "normal" range. In fact, only three cases of heart disease (cases 85, 88 and 95) showed elevated values. These results are not in agreement with the findings of Raab and Gigee[26] who report elevated mean values for cases of myocardial hypertrophy and congestive heart failure. The significance of the tissue catechol amine concentration remains speculative. At least in the normal person the major portion of the heart catechol amines is produced at the sympathetic nerve endings within the heart. The rates of local degradation and excretion remain indefinite. Thus the metabolism of the catechol amines could be increased despite a low tissue level. Certainly the demonstration of increased urinary catechol amine excretion in hypertension and myocardial infarction suggests an increased catechol amine metabolism in these conditions. Our studies contribute little to the problem of ventricular irritability. It is difficult to evaluate the only case of ventricular fibrillation (case 61) because of postmortem epinephrine injection. However, this assay value was the highest recorded in the series.

Renal Insufficiency. In 12 cases the blood urea nitrogen ranged from 50 to 100 mg. per 100 ml. The hearts from this group showed a mean tissue catechol amine concentration of 0.43 μg. per Gm. There were six cases in which the blood urea nitrogen was elevated above 100 mg. per 100 ml. The mean for the second group was 0.10 μg. per Gm. The highest value was 0.27 μg. per Gm. while all other values were below 0.14 μg. per Gm.

One might anticipate catechol amine retention in renal insufficiency in view of the known renal excretion of these hormones.[29] Our data show a slight mean elevation for the cases with a blood urea nitrogen between 50 and 100 mg. per 100 ml. However, most cases in this first group do not have a true renal insufficiency, but suffered from other disease states causing a mild extrarenal azotemia. On the other hand, cases with a blood urea nitrogen above 100 mg. per 100 ml. give a low mean value. Most cases of uremia showed a low value and not a single case exceeded the normal range. These findings do not agree with those of Raab and Gigee[26] who found elevated values in the blood and hearts of patients with uremia.

Adrenalectomy. Current data do not permit a definite conclusion as to the role played by the adrenal medulla in the production of catechol amines normally found in the heart. Case 7 was totally adrenalectomized two months before death. The presence of a slightly elevated heart catechol amine concentration at death shows that the adrenal medulla is not necessary for the maintenance of the heart catechol amine concentration.

Our studies extending over a period of three years and including the 100 cases reported here and an additional 120 cases assayed by a different method and to be reported later have failed to uncover a single case of sudden death which could be attributed to excessive myocardial catechol amine concentration. Although death can be caused by injection of massive quantities of catechol amines, still their significance in unexplained sudden death seems questionable. Probably the circulating level of catechol amines never reaches the concentration needed to cause death except perhaps in the case of pheochromocytoma. Surprisingly enough in cases of pheochromocytoma the circulating level of catechol amines is often quite high for many weeks, months, or years without causing death.

Summary

The tissue catechol amine concentration of 100 human hearts was determined by the aluminum hydroxide-arsenomolybdic acid method. Intravenous injection of norepinephrine or intracardiac injection of epinephrine caused a marked elevation in the tissue

catechol amine concentration of the heart. Total (bilateral) adrenalectomy did not reduce the tissue catechol amine concentration of one heart. Twenty-one cases showed significant elevation of the tissue catechol amine concentration of the heart. However, no disease state produced a consistent elevation of the assay value. We were unable to show an elevation of the tissue catechol amine concentration of hearts from cases of cardiovascular disease or uremia, as previously reported. In fact, there was a significant depression in the catechol amine concentration of the hearts from 5 of 6 cases with uremia.

Acknowledgment

We are indebted to Mr. C. V. Sittler and Mr. R. F. Blythe for technical assistance.

Summario in Interlingua

Le histoconcentration de catechol-amina in 100 cordes human esseva determinate per medio del methodo a hydroxydo de aluminium e acido arsenomolybdic. Injectiones intravenose de norepinephrina o intracardiac de epinephrina non causava un marcate elevation del histoconcentration de catechol-amina del corde. Bilatere adrenalectomia total non reduceva le histoconcentration de catechol-amina del corde. Vinti-un casos monstrava significative elevationes del histoconcentration de catechol-amina del corde. Nonobstante, nulle stato morbose produceva un elevation regular del valores obtenite. Nos non succedeva a demonstrar un elevation del histoconcentration de catechol-amina del corde in casos de morbo cardiovascular o de uremia, in contrasto con lo que esseva previemente reportate per alteros. De facto, il habeva un significative depression del histoconcentration de catechol-amina del corde in cinque inter sex casos de uremia.

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Vectorcardiographic Notation

By ROBERT A. HELM, M.D.

The method of viewing the frontal, sagittal and transverse vectorcardiographic planes is considered from the standpoint of devising a uniform system of measuring angles on these planes. It is pointed out that care must be taken in the selection of oscilloscopic presentations to prevent inconsistency of the signs of the trigonometric functions of such angles. Two groups of oscilloscopic presentations are suggested, either of which permits angles to be measured in a clockwise direction from a reference axis of uniform position on each plane.

IT is highly desirable that universal agreement be reached concerning the use of certain terminology and notation in vectorcardiography. Toward this end, the Committee on Electrocardiography of the American Heart Association has recently recommended standard designations for vectorcardiographic axes and planes and uniform methods of displaying planar vectorcardiograms.[1] Briefly, in accordance with the Committee's recommendations, the three rectilinear coordinate axes of the body, transverse, longitudinal and sagittal, are to be designated by the symbols x, y and z, respectively. The three planes defined by these rectilinear coordinates, transverse, frontal and sagittal, are to be designated by the symbols xz, xy and yz, respectively. The frontal plane is to be viewed by an observer facing the anterior aspect of the upright subject. The sagittal plane is to be viewed by an observer facing the left lateral aspect of the upright subject. An alternate sagittal view, which the Committee deems less desirable, is from the upright subject's right side. The transverse plane is to be viewed by an observer facing the head of the prone subject. An alternate, but, in the Committee's opinion, less desirable transverse view, consists of having an observer face the feet of the supine subject. A diagram of the Committee's preferred planar displays is illustrated in figure 1.

The Committee devotes considerable space to a consideration of the concept of polarity in that portion of its report dealing with vectorcardiography.[1] Much of the confusion concerning polarity, heretofore apparent in vectorcardiographic literature, can be avoided in the future if this section is carefully read by all investigators in this field. The writer is in full agreement that the movement of the cathode ray during vectorcardiographic recording should be defined by designating the deflection plates of the oscilloscope in accordance with the anatomic aspects of the subject to which they are connected, and that such a definition does not involve consideration of polarity. Nevertheless, as will be pointed out in detail later, the concept of polarity emerges indirectly as the result of the necessity of dealing with the signs of the trigonometric functions of an angle formed by a vector, located in one of the various quadrants of a plane.

To date, the Committee has published no recommendations concerning the manner of measuring and designating angles on the three planes. The method of making such measurements on the frontal or xy plane has been firmly established by Einthoven, and others since, who have measured a positive angle, alpha, by rotating a vector clockwise* about the z axis, the (subject's) left end of the x axis being designated as 0 degrees. Such a vector may be rotated through 360 degrees to avoid the use of negative angles, or it may be rotated either clockwise or counterclockwise from the

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* The conventional mathematical rotation of such a vector is in a counter-clockwise direction. Einthoven reversed this convention in order that the majority of QRS and T vectors might fall in the first rather than in the fourth quadrant. Bayley[2] advocated a return to the conventional notation, but his suggestion has not been generally accepted.

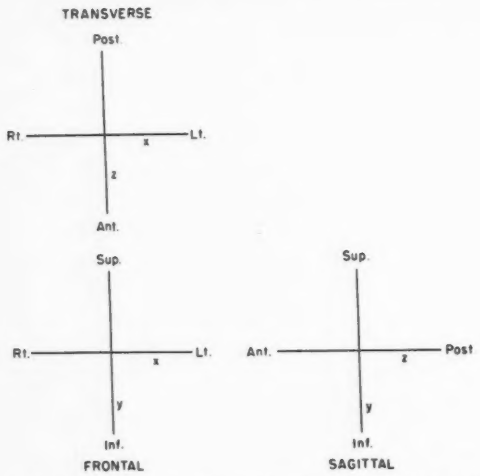

FIG. 1. Vectorcardiographic views advocated and preferred by the Committee on Electrocardiography and Vectorcardiography of the American Heart Association.

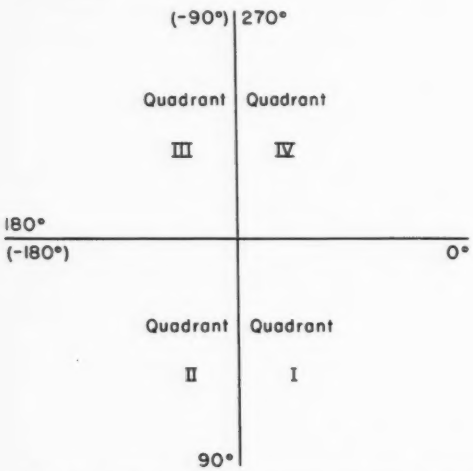

FIG. 2. Clockwise method of measuring angles, first applied by Einthoven to the frontal plane. See text.

left end of the x axis, designated as 0 degrees, to the right end of the x axis, designated as ±180 degrees. These manipulations may be clarified by superimposing figure 2 on the frontal plane view illustrated in figure 1.

Parenthetically, it should be mentioned that the author, with Fowler, devised a method of measuring angles on all three planes in order to study certain vectorcardiographic data statistically. This method, described in detail

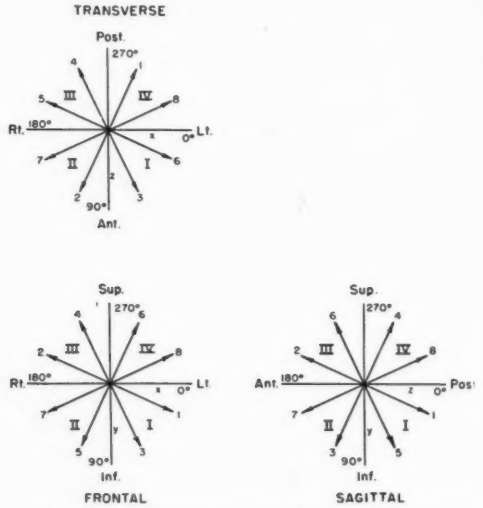

FIG. 3. Diagram of vectors, one of which extends into each octant. See text and table 1.

elsewhere,[3] was chosen because it permitted a separate coordinate axis to be used for the reference or 0 degree axis of each plane.† Although this reference notation did not involve inconsistencies of the signs of trigonometric functions, it is the writer's present opinion that the lack of a uniform position for the reference or 0 degree axis in the three planes is undesirable.

Faced with the problem of designating angles on planes other than the frontal, most vectorcardiographers superimpose figure 2 on such planes whether the latter be viewed from left or right (sagittal) or from head or foot (transverse). Let us consider the Committee's preferred presentations of the three planes illustrated in figure 1, when figure 2 is superimposed on each. Each plane is then divided into quadrants and, as a result, the spatial coordinate frame is divided into octants involving all possible combinations of the three pairs, right and left, superior and inferior, and anterior and posterior. Let us assume that a vector is directed from the point of intersection of the coordinate axes into each of the octants. These vectors are numbered 1 through 8 in

† The general method of deriving the equations given in that paper[3] are not dependent upon this specific notation. The equations can easily be modified to conform to any notation chosen.

gure 3 and in table 1. The octant into which ach of the eight vectors is directed, is desig- ated by the appropriate symbols in the second olumn of table 1. It should be noted from gure 3 that each quadrant of each plane con- ains two vector projections. Although up until he present point in the discussion, nothing has een said or implied concerning polarity of the , y, and z coordinate axes, it is no longer ossible to avoid a consideration of polarity. The magnitude and direction of a vector, lying n the *first* quadrant (0 to 90 degrees) of a lane, is defined in terms of its two rectilinear oordinates, both of which must be positive. Similarly, a vector in the *third* quadrant (180 to 270 degrees) is defined in terms of coordinates which are both negative. For a vector in the *second* quadrant (90 to 180 degrees), one coordinate is positive and the other negative, and these conditions are completely reversed for a vector in the *fourth* quadrant (270 to 360 or 0 degrees). These are inescapable facts based upon well established geometric and trigonometric conventions. In fact, the signs of the trigonometric functions are wholly dependent upon the quadrant occupied by the rotating vector forming the angle. From these considerations the signs of the x, y and z coordinates defining each of the eight vectors, one in each octant, are listed in table 1, based on the quadrants of the *frontal and sagittal planes* occupied by the vector projections. Finally, in the last two columns of table 1 are listed the signs of the x and z coordinates based on the quadrants of the *transverse plane* occupied by each of the vector projections. It should be noted that there is a complete discrepancy between the signs of the z coordinates based upon the frontal and sagittal planes on the one hand and upon the transverse plane on the other.

TABLE 1.—*Discrepancy of signs resulting from application of Einthoven's frontal plane convention to the sagittal and transverse planes of figure 1*

Vector	Location* of Vector	Frontal and Sagittal			Transverse	
		x	y	z	x	z
1	L, I, P	+	+	+	+	−
2	R, S, A	−	−	−	−	+
3	L, I, A	+	+	−	+	+
4	R, S, P	−	−	+	−	−
5	R, I, P	−	+	+	−	−
6	L, S, A	+	−	−	+	+
7	R, I, A	−	+	−	−	+
8	L, S, P	+	−	+	+	−

* L = left, R = right, I = inferior, S = superior, P = posterior, A = anterior.

How may this mathematic invalidity be circumvented? If the method of viewing the planes (fig. 1), preferred by the Committee, is to be retained, there is only one general solution. The method of measuring Einthoven's angle alpha, so well established for the frontal plane, must be sacrificed in at least one of the two remaining planes. Thus, either of the changes illustrated in figure 4*A* or in figure 4*B*

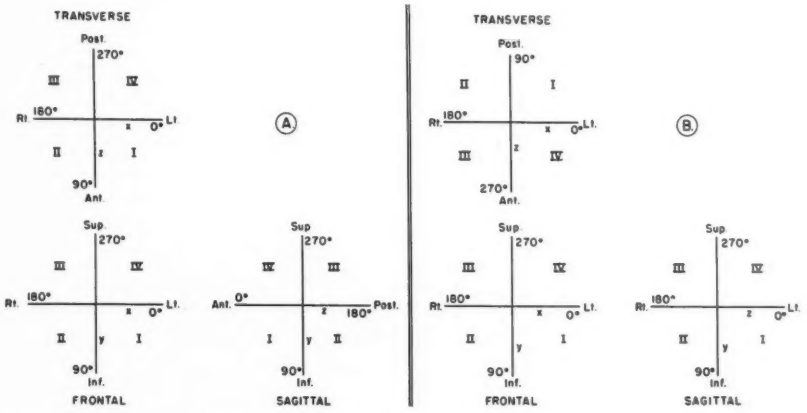

FIG. 4. Modification of method of making angular measurements to prevent inconsistency of trigonometric signs. See text.

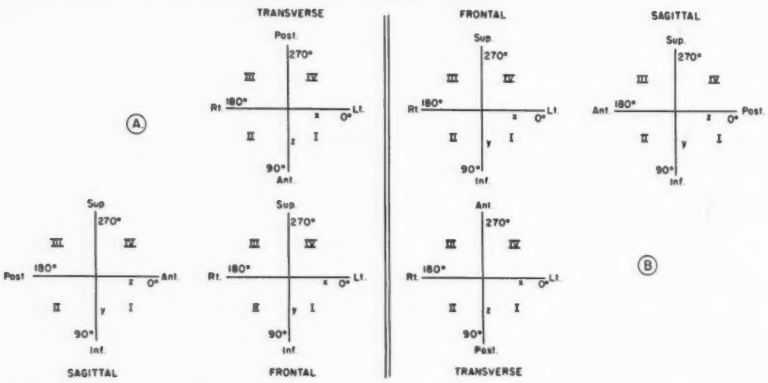

FIG. 5. Modification of method of viewing planes to prevent inconsistency of trigonometric signs. See text.

would correct the discrepancy of sign noted in table 1.

Although the notations depicted by figures 4*A* and *B* are mathematically valid, they are quite objectionable from the standpoint of symmetry of presentation. It would be most desirable to measure all angles in a uniform direction of rotation from a reference axis of uniform position in all three planes. To accomplish this feat in the simplest manner possible, the position of the observer of the sagittal plane in figure 4*A* may be rotated 180 degrees about the y axis. Similarly, the position of the observer of the transverse plane in figure 4*B* may be rotated 180 degrees about the x axis. Thus, figure 5*A* differs from figure 4*A* in that the sagittal plane is viewed from the upright subject's right side rather than from his left side. Figure 5*B* differs from figure 4*B* in that the transverse plane is viewed from the feet of the supine subject rather than from the head of the prone subject. A table similar to table 1 could be constructed for either figure 5*A* or *B*, without encountering any discrepancy of sign.* Either group of oscilloscopic presentations could be chosen as standard without invalidating any of the Committee's recommendations,[1] for it is obvious that in figures 5*A* and *B*, respectively, the Committee's *alternate* sagittal and transverse views are utilized. However, one minor alteration of the Committee's recommendations might be suggested. It would seem desirable to designate the reference or 0 degree axis for measuring angles on a given plane by listing the symbol for that axis initially in the double symbol nomenclature of planes. Thus, in both figure 5*A* and *B* (as well as in fig. 4*A* and *B*) the frontal, sagittal and transverse planes might preferably be designated respectively as xy, zy and xz, rather than as xy, yz and xz, suggested by the Committee.

* Unlike the notation previously used,[3] the axes of the oscilloscopic presentations illustrated in figures 5*A* and *B* (as well as in figs. 4*A* and *B*) do not consistently form either a right-handed or a left-handed frame (see Braunstein,[4] fig. 1). However, the author can envisage no practical difficulty arising from this discrepancy and considers that the convenience of a uniform position of the reference axis, and of a uniform direction of angular measurement, greatly outweighs any theoretic objection to it.

SUMMARY

In the writer's opinion, it is highly desirable that angles be measured in a uniform direction of rotation on the frontal, sagittal, and transverse vectorcardiographic planes and that the reference or 0 degree axis be located in a uniform position on each of these planes. Furthermore, it would be most desirable to retain Einthoven's well-established frontal plane convention of a clockwise direction of rotation for a positive angle with the reference or 0 degree axis corresponding to the (subject's) left end of the x axis, i.e., lead I in Einthoven's scheme. It is pointed out that the oscilloscopic views advocated and *preferred* by the Committee on Electrocardiography and Vectorcardiography of the American Heart Association

are mathematically incompatible with the extension of Einthoven's frontal plane convention to *both* the sagittal and transverse planes. (See fig. 3 and table 1.) However, if an *alternate* sagittal or transverse plane presentation, either of which is permitted but not preferred according to the recommendations of the Committee, is selected, Einthoven's frontal plane convention may be applied to these planes without any discrepancy of trigonometric sign. For this reason, it is suggested that one or the other of the groups of oscilloscopic presentations illustrated in figure 5*A* or *B* be considered for universal adoption. If either is chosen, it is further suggested that the frontal, sagittal and transverse planes be represented respectively by the symbols xy, zy and xz, in order that the first term of the paired symbols might designate the reference axis of the respective plane.

Summario in Interlingua

Le methodo de visualisar le planos vectocardiographic frontal, sagittal, e transverse es considerate in connexion con le problema de elaborar un systema uniforme pro le mesuration de angulos in le planos mentionate. Es signalate le necessitate de grande attention in seliger presentationes oscilloscopic, a fin de prevenir inconsequente signos in le functiones trigonometric de tal angulos. Nos propone duo gruppos de presentationes oscilloscopic. Ambes permitte le mesuration de angulos in un direction dextrorse ab un axe de base con position uniforme in omne planos.

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Hemolytic Syndrome Following the Insertion of a Lucite Ball Valve Prosthesis into the Cardiovascular System

By Frederick Stohlman, Jr., M.D., Stanley J. Sarnoff, M.D., Robert B. Case, M.D. and Arthur T. Ness, Ph.D.

Permanent bypass of the aortic valve was accomplished in the dog by placing a lucite conduit containing a Hufnagel valve between the left ventricular apex and thoracic aorta. Red cell destruction was produced by the valve in this position and was accompanied by hemoglobinemia, hemoglobinuria, anemia, reticulocytosis and renal hemosiderosis. Red cell survival, as determined with Cr^{51}, was markedly shortened.

THE development of a lucite ball valve prosthesis by Hufnagel[1] has made possible significant advances in the field of cardiac surgery. This prosthesis originally was inserted in the thoracic aorta distal to the left subclavian artery in an effort partially to correct the regurgitation of aortic insufficiency. More recently an operation for the correction of an artificially induced aortic stenosis in the dog with a prosthesis containing such a lucite ball valve* has been described by Sarnoff, Donovan, and Case.[2] The prosthesis was inserted between the apex of the left ventricle and the thoracic aorta. Following this procedure the cardiac output (minus coronary flow) enters the aorta via the apical-aortic anastomosis. During the course of postoperative studies it was noted that these dogs developed hemoglobinemia, hemoglobinuria, and anemia. Preliminary observations have been reported elsewhere.[3] In this paper observations on the red blood cell destruction occurring after insertion of the lucite ball valve prosthesis are reported.

Methods and Materials

Studies have been carried out on a total of 15 dogs; in 8 dogs throughout their postoperative course and in 12 dogs at periods from one to 10 months postoperatively. The dogs weighed from 16 to 25 Kg. The description of the prosthesis and technic of insertion has been published previously.[2] Hematocrits were determined by the method of Strumia[4] and reticulocytes were stained with new methylene blue,[5] and enumerated as described by Brecher and Schneiderman.[6] Plasma hemoglobin was determined by the method of Bing and Baker.[7] Normal values in this laboratory are 40 to 55 per cent for the hematocrit and 0.1 to 0.7 per cent for the reticulocyte count. Plasma hemoglobin, collected in the manner used in this study, was found to be up to 20 mg. per 100 cc. in control dogs. Significance was not attributed to plasma hemoglobin levels of less than 30 mg. per 100 cc. Urine was tested for hemosiderin with the Prussian-blue reaction. The methods employed in the estimation of red cell survival with Cr^{51} following auto- and homo-transfusion and the data on which normal values in the dog are based are given elsewhere.[8] Donors and recipients were compatible for the known canine agglutinogens.[9]

Results

All 15 dogs studied showed evidence of increased red cell destruction following the introduction of the lucite ball valve prosthesis in the apical-aortic position.

(1) *Changes in Hematocrit, Reticulocyte Count, and Plasma Hemoglobin During the Postoperative Period.* Eight dogs have been followed for 5 to 84 days after operation. The changes shown in figure 1 are representative of the ranges encountered in this group. In the first 6 to 10 days, a sharp decline in hematocrit occurred in all dogs except dog 15 (fig. 1). Thereafter the course varied. In two dogs, the hematocrit rose briefly and then declined to

From the Laboratory of Pathology and Histochemistry of the National Institute of Arthritis and Metabolic Diseases and the Laboratory of Cardiovascular Hemodynamics, National Heart Institute, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.

* Made by Mr. Carl Hewson, Brunswick Manufacturing Co., Roxbury, Mass.

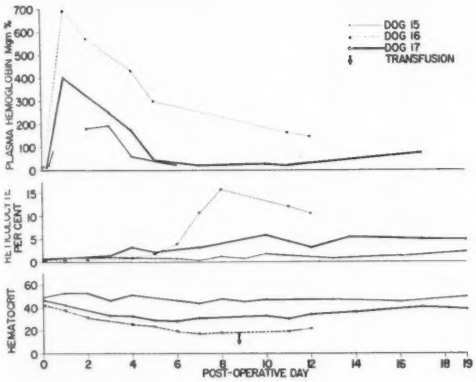

FIG. 1. Changes in hematocrit, reticulocytes, and plasma hemoglobin during the immediate postoperative period after insertion of an apical-aortic anastomosis containing a lucite ball valve.

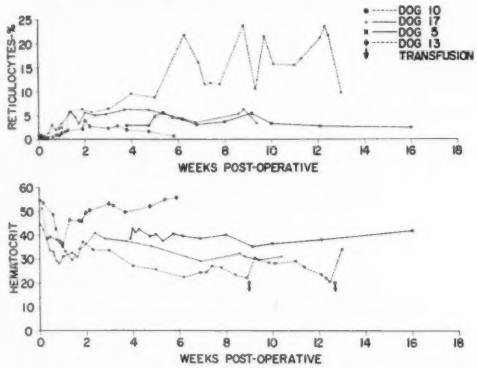

FIG. 2. The course of the anemia in four dogs following insertion of an apical-aortic anastomosis. Dog 17 subsequently had a further decline in hematocrit and required transfusions.

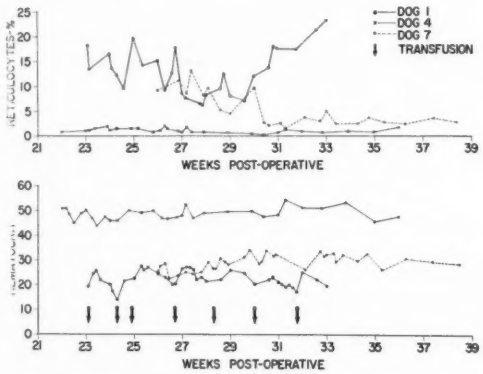

FIG. 3. The course of the anemia 5 to 10 months after insertion of the apical-aortic anastomosis.

levels of 20 to 25. These dogs subsequently required transfusion for survival (dogs 10 and 17, fig. 2). In two other dogs the hematocrit stabilized between 30 and 35. One dog showed a return to normal values (dog 13, fig. 2). Two dogs died after operation, one on the fifth day and the other on the twelfth, with hematocrits of 33 and 17, respectively, (dog 16, fig. 1).

Reticulocytosis became apparent on the third to the fifth day in all eight dogs studied. There was a close correlation between the severity of anemia and the degree of reticulocytosis (figs. 1, 2 and 3).

Striking hemoglobinemia and hemoglobinuria, indicating intravascular hemolysis, were observed in all dogs. Maximum plasma hemoglobin levels varying from 180 to 800 mg. per 100 cc. were observed on the first or second postoperative day in the six dogs in which it was determined.

In addition to the studies mentioned above, a simple 2-inch lucite tube was substituted for a segment of thoracic aorta in four dogs. A slight and transient reticulocytosis and fall in hematocrit, compatible with blood loss incident to operation, were observed following this procedure. Plasma hemoglobin levels remained below 10 mg. per 100 cc.

(2) *Long Term Observations on the Course of Anemia.* The course of the anemia in seven dogs for periods up to 10 months are shown in figures 2 and 3. These are representative of the 12 dogs so studied. It is evident that red cell destruction by the valve continued over the period of observation and that there was a considerable variability in this phenomenon. Reticulocyte values remained elevated above the normal of 0.1 to 0.7 per cent even in those dogs in which the hematocrit had returned to normal. Transfusion has been required (figs. 2 and 3) at frequent intervals to maintain three of the dogs studied.

In those dogs with more severe hemolytic states, plasma hemoglobin values ranging from 75 to 280 mg. per 100 cc. were observed throughout the period of study. In those dogs whose hematocrits were above 35, intermittent hemoglobinemia has been observed with values ranging up to 75 mg. per 100 cc. Gross hemosiderinuria has been observed in all dogs.

FIG. 4. Iron stain of the kidney of a dog nine months after the insertion of the apical-aortic anastomosis. The dark staining material in the tubules is iron.

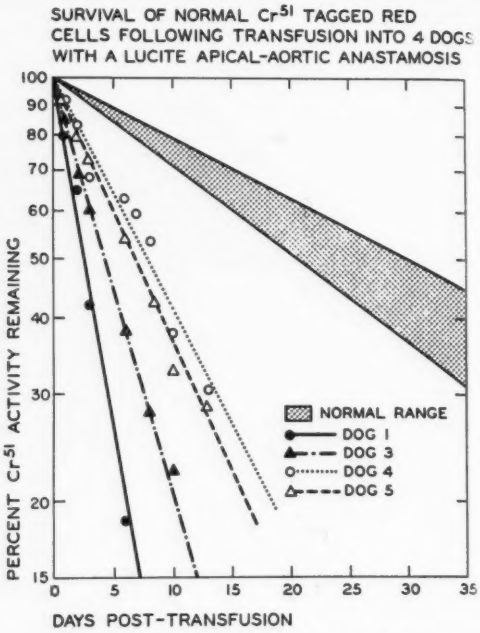

FIG. 5. Red cell survival in four dogs determined three weeks to seven months after insertion of the apical-aortic anastomosis. Cr^{51} values are plotted on a semilogarithmic scale.

Three dogs died nonrenal deaths during the period of study and a fourth died of unknown causes. In these four dogs, whose hematocrits were 20, 22, 37 and 45, heavy deposits of hemosiderin were found in the kidney, primarily in the proximal convoluted tubule (fig. 4).

(3) *Red Cell Survival.* Shortened red cell survival furnished further evidence of hemolysis. Survival of normal red cells from a single compatible donor was studied in six dogs at periods of three weeks to seven months following insertion of the prosthesis. Hematocrit values in these animals ranged from 20 to 47. In figure 5, the survival of normal donor cells in four of these animals is shown. The survival of red cells in the two other dogs was almost superimposable on the curves of dogs 1 and 3. It is evident that there is marked shortening of survival, the apparent half time varying from 3 to 10 days as compared with the normal value of 21 to 30 days (8). Estimates of the rate of random loss of Cr^{51} per day from hemolysis and elution ranged from 7 to 25 per cent. Normally there is an elution of 1 to 2 per cent of the remaining Cr^{51} from the surviving cells.[8] Red cell survival following autotransfusion was also shortened in the three dogs so studied. From these data it is clear that, on the average, the rate of red cell destruction was increased several fold.

TABLE 1.—*Correlation of Red Cell Survival, Hematocrit and Reticulocyte Count in Six Dogs with a Lucite Apical-Aortic Anastomosis*

Dog No.	Apparent Cr^{51} Half-time Days	Hematocrit %	Reticulocyte Count %
1	3.0	21.0	15.0
7	3.0	25.0	9.6
3	4.5	34.5	3.5
6	5.0	30.8	8.2
5	7.0	39.8	4.1
4	10.0	48.5	1.25

Hematocrit and reticulocyte count are expressed as mean values during the period of study of red cell survival.

As might be expected there was a correlation between the severity of the anemia and the shortening of apparent red cell half time (table). This relationship is consonant with the evidence presented in the foregoing sections, namely that the anemia is a consequence of shortened red cell survival.

Discussion

An increased rate of red cell destruction has been found in all dogs following the insertion of a lucite apical-aortic anastomosis containing a Hufnagel ball valve. The evidence for hemolysis has consisted of a postoperative fall in hematocrit, reticulocytosis, and a shortened red cell life span, accompanied by hemoglobinemia, hemoglobinuria, and hemosiderinuria. There were also heavy tubular deposits of hemosiderin in the kidneys. The degree of hemolysis has varied in severity. Where the hemolytic process was relatively mild, the increased rate of production of red cells was sufficient to compensate for the hemolysis and the hematocrit returned to normal following the initial decline. In the others anemia has persisted accompanied by marked reticulocytosis, hemoglobinemia, and in some instances, hemoglobinuria.

There is little doubt that hemolysis in these animals is related to the prosthesis. It appears likely that red cells traumatized by contact between the rigid ball and rigid valve housing are damaged or destroyed. Since hemoglobinemia is present, it is evident that many of these are destroyed intravascularly; perhaps others suffering less damage at the time of impact may be removed extravascularly. The possibility was considered that chemical injury to the red cell resulting from contact with some constituent of the plastic accounts for the hemolysis. However, the results of studies on dogs following the insertion of a simple lucite tube in the aorta are inconsistent with the latter explanation.

Many factors undoubtedly play a role in establishing the rate of hemolysis in an individual dog. Older cells which are mechanically more fragile,[10] are undoubtedly destroyed more rapidly and this at least in part may account for the peak hemoglobinemia occurring in the immediate postoperative period. Subsequently there are few cells greater than 50 days old and difference in fragility, due to age of cells, is probably of less importance. The difference in survival of blood from a single donor in six recipients with valves would seem to exclude the inherent fragility of the red cell as a significant factor.

Other factors, such as the magnitude and the rate of change of the pressure gradient across the valve, which determine the impact force of the ball, are of greater significance. When the conventional Hufnagel valve is placed in the descending aorta for the treatment of aortic insufficiency, it may be expected that the impact force of the ball will be less, and thereby the extent of hemolysis correspondingly diminished. Nevertheless a fall in hematocrit was noted by Rose and coworkers[11] in nine patients in whom the conventional Hufnagel valve had been inserted for aortic regurgitation. The hematocrit on an average fell to 34.8 from a preoperative level of 41.5. It is likely that these were not the lowest hematocrits exhibited by these patients since these values were determined between the fourteenth and thirty-sixth postoperative day (average 24.2). It is a safe assumption that by the fourteenth day increased red cell production had already begun to compensate for the induced anemia (fig. 2). Alterations in plasma volume were not responsible for the lowered hematocrits since in those patients there was no significant change of plasma volume. It seems reasonable to suggest on the basis of the present report that an increased rate of red cell destruction may be responsible for at least a part of the postoperative decline in hematocrit.

It has recently been made clear[12] that one of the important compensatory responses to anemia is coronary vasodilation and a consequent increase in coronary flow to provide the oxygen required by the myocardium. It was also demonstrated that, in the presence of coronary insufficiency, degrees of anemia which are ordinarily well tolerated by the myocardium depress myocardial function. The frequency with which angina pectoris presents itself as a prominent part of the symptom complex in aortic regurgitation together with the known

low aortic diastolic (coronary perfusion) pressures make it very likely that coronary insufficiency is an important component in this disease. It is suggested, therefore, that in these patients even slight degrees of anemia be carefully avoided.[16] This should be particularly watched for in the immediate postoperative period after the placement of the Hufnagel valve, especially since coronary perfusion pressure is substantially decreased following this procedure.[11, 13, 16] Put in other terms, the coronary vessels should not be required to dilate in response to anemia, whatever the cause may be, when in all likelihood, they are already maximally dilated because of the low coronary perfusion pressure.

Data collected subsequent to the investigations cited above appear to clarify certain aspects of the overall problem. Some of the apical-aortic prostheses which had been used in the above experiments were segmented so as to obtain conventional Hufnagel valves. These were then placed in the thoracic aorta below the left subclavian artery in dogs in which moderate aortic insufficiency had been produced.* In 3 of the 5 dogs studied there was a mild increase in the rate of red cell destruction. In these dogs the insufficiency proximal to the valve was moderate whereas in those with the apical-aortic by-pass there was virtually complete insufficiency proximal to the valve. Thus, the position of the ball-valve in large measure determines its effect on the survival of red cells. Presumably, the degree of insufficiency which determines the rate of change of the pressure gradient across the valve and, therefore, its velocity and impact force upon seating, is the determining factor. The rate of change of the pressure gradient across the valve and the consequent impact force of the ball would be even greater in the atrioventricular position.

The above data do not in any way constitute a contraindication to the use of the lucite ball-valve prosthesis in the conventional Hufnagel position provided that the immediate postoperative decline in hematocrit be avoided. They do, however, strongly suggest that the lucite ball-valve is unsuitable for use in direct continuity with cardiac chambers.

More recent efforts have been devoted to the development of an elastic silicone valve[14] in the hope that the more resilient housing would absorb some of the impact force of the ball. The data thus far are encouraging and indicate a substantial decrease in red cell destruction to a level which may be satisfactory for clinical use in the apical-aortic position.[15]

* The authors gratefully acknowledge the assistance of Drs. I. K. R. McMillan and Joseph Roshe in connection with this aspect of the investigation.

Summary

The insertion of a lucite prosthesis containing a Hufnagel ball valve between the apex of the left ventricle and the thoracic aorta has led to the development of an anemia, accompanied by hemoglobinemia, hemoglobinuria, hemosiderinuria and a markedly shortened red cell life span. The hemolytic process apparently results from mechanical trauma to the red cells by the impact of the rigid ball against the rigid valve housing. Such a valve is not suitable for use in direct continuity with the cardiac chambers.

Summario in Interlingua

Le placiamento del valvula aortic in derivation permanente esseva effectuate in canes per le installation de un conducto de Lucite, continente un valvula de Hufnagel, inter le apice sinistro-ventricular e le aorta thoracic. Le valvula causava destruction de erythrocytos. Isto esseva accompaniate de hemoglobinemia, hemoglobinuria, anemia, reticulocytosis, e hemosiderosis renal. Le superviventia del erythrocytos, determinate per medio de Cr^{51}, esseva marcatemente reducite. Un tal valvula non es usabile in continuitate directe con le cameras cardiac.

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A Two-Dimensional Ballistocardiographic Study of the Relation of Body Size to Ballistic Amplitude in Children

By GWENDOLYN L. MORRIS, M.D. AND MELVILLE I. SINGER, M.D.

Simultaneous longitudinal and transverse ballistocardiograms were obtained from 20 normal boys and 20 normal girls ranging in age from 4 to 15 years. A highly significant correlation was found to exist between body surface area and the basal mean IJ amplitude.

CONSIDERABLE doubt has existed in regard to the value of the ballistocardiogram for determining cardiac output. The formulas in use at the present time assume that the stroke volume is roughly proportional to the amplitude of the IJ segment. Taylor and Tiede[1] concluded that the high-frequency ballistocardiogram is measuring something only indirectly related to the cardiac output, since the results of their study indicated that the instrument gives estimates of cardiac output which do not distinguish between large and small individuals. In a recent publication, Morris and Braunstein[2] were able to demonstrate a significant correlation between body surface area and IJ amplitude in a group of 41 normal male adults. The mean body surface area of this group was 1.85 square meters with a standard deviation of 0.14. Having found that this relationship existed for adults, we were interested in obtaining high-frequency basal ballistocardiograms from children to determine whether or not such a significant correlation existed for individuals of small body size.

With the exception of studies of coarctation of the aorta, little material has been published in regard to ballistocardiograms obtained from children. We have been interested in evaluating the usefulness of the ballistocardiograph in the study of congenital heart disease, particularly in children with shunts such as patent ductus arteriosus and septal defects. This study is in progress at the present time. However, it is first necessary to establish normal standards for the young age group.

MATERIAL AND METHOD

The subjects tested in this study were taken from the wards of the Children's Hospital of Cincinnati and the pediatric wards of the Cincinnati General Hospital. The 40 children who constitute the study group had been admitted to the hospitals for elective surgical procedures or medical illnesses. Ballistocardiograms were obtained only after all evidence indicated that recovery was complete. All the children in the study were found free of cardiac or respiratory disease as indicated by normal physical examination, chest x-ray films, electrocardiograms, and hematologic determinations.

The 20 boys in the study group ranged in age from 5 to 15 years. The 20 girls who were studied ranged in age from 4 to 14 years.

Simultaneous longitudinal and transverse records were taken on a high-frequency ballistocardiograph which has been described in previous publications.[3] All the tracings were taken with the subjects in the postabsorptive state and after they had rested for 15 minutes upon the table.

The average IJ amplitude was determined by measuring and averaging the IJ amplitude from three consecutive respiratory cycles of the longitudinal tracings. Observed cardiac force, expected cardiac force and critical ratio were determined for each subject according to the formulas devised by Starr.[4]

Body surface area was determined on the basis of height and weight using a nomogram based on the formula of DuBois.[5]

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Dr. Morris is a Trainee of the National Heart Institute.

TABLE 1.—*Data Obtained from 20 Normal Boys*

Subject	Age	Height (inches)	Weight (lbs.)	B.S.A. (M^2)	Average IJ Amplitude	Cardiac Force		Critical Ratio
						Observed	Expected	
1. G.P.	12	57.50	77.50	1.21	6.6	13.2	15.20	.31
2. L.D.	6	48.50	50.00	0.89	7.5	15.0	7.65	1.15
3. D.F.	7	45.00	46.50	0.82	6.7	13.9	6.00	1.23
4. H.W.	7	49.50	53.00	0.93	10.2	20.8	8.60	1.91
5. R.F.	6	41.00	36.00	0.65	6.3	12.7	1.99	1.67
6. W.H.	11	54.50	77.00	1.16	12.0	23.5	14.02	1.48
7. R.K.	12	55.75	79.00	1.19	10.1	20.0	14.73	.82
8. C.L.	5	44.50	43.50	0.78	5.5	11.1	5.06	.94
9. C.W.	10	60.25	83.00	1.28	13.4	26.7	16.85	1.53
10. R.W.	13	58.50	82.00	1.25	11.4	22.3	16.15	.96
11. S.P.	10	50.00	49.75	0.90	10.0	19.8	7.89	1.86
12. R.P.	6	48.00	45.00	0.84	5.0	10.7	6.47	.66
13. N.A.	15	59.50	72.00	1.20	7.7	15.5	14.97	.08
14. J.R.	7	48.00	55.00	0.92	2.8	5.8	8.36	.40
15. V.I.	6	47.75	45.50	0.84	3.0	6.2	6.47	.04
16. W.G.	9	54.00	65.00	1.08	7.9	15.8	12.14	.57
17. T.H.	11	48.50	81.00	1.10	12.4	24.7	12.61	1.89
18. R.C.	5	57.00	44.50	0.94	5.9	12.0	8.83	.49
19. R.R.	7	51.00	62.50	1.00	5.1	10.5	10.25	.04
20. W.G.	12	63.00	103.25	1.45	16.7	33.7	20.87	2.01

TABLE 2.—*Data Obtained from 20 Normal Girls*

Subject	Age	Height (inches)	Weight (lbs.)	B.S.A. (M^2)	Average IJ Amplitude	Cardiac Force		Critical Ratio
						Observed	Expected	
1. L.D.	8	51.12	61.75	1.01	9.55	19.30	10.48	1.37
2. M.G.	12	56.00	92.00	1.28	10.63	21.80	16.85	0.77
3. M.J.	12	58.25	78.25	1.22	7.28	15.00	15.44	0.07
4. C.K.	10	50.50	49.00	0.90	2.60	5.16	7.89	0.43
5. B.K.	10	48.00	57.50	0.94	8.09	16.00	8.83	1.12
6. M.L.	10	52.75	66.50	1.06	3.45	6.80	11.66	0.75
7. L.B.	11	53.00	63.00	1.04	3.27	6.7	11.19	0.70
8. R.W.	14	63.50	117.75	1.55	4.35	8.7	23.23	2.27
9. K.R.	8	48.00	59.00	0.94	5.00	10.6	8.83	0.28
10. A.S.	11	56.50	71.50	1.16	8.53	17.3	14.02	0.51
11. J.V.	8	48.50	44.00	0.84	2.45	4.8	6.47	0.26
12. L.P.	8	57.00	64.00	1.11	3.12	6.4	12.84	1.00
13. M.M.	13	59.00	77.25	1.23	4.22	9.0	15.67	1.04
14. H.N.	7	44.25	34.25	0.74	3.64	6.0	4.11	0.29
15. B.M.	4	39.00	35.00	0.65	1.92	4.4	1.99	0.38
16. B.H.	10	61.00	128.00	1.56	12.07	23.1	23.46	0.06
17. N.R.	4	36.00	33.50	0.60	3.67	7.5	0.81	1.04
18. B.C.	12	59.00	82.50	1.26	9.72	18.8	16.38	0.38
19. I.H.	11	61.50	93.00	1.37	12.25	24.8	18.98	0.91
20. P.W.	9	48.00	55.00	0.92	6.00	12.5	8.46	0.63

TABLE 3.—*The t Values for Regressions of IJ Amplitude on Body Surface Area in the Two Sexes*

	Body Surface Area	
	Males	Females
Basal long. IJ amplitude....	4.4525*	3.3150†

* $p < 0.001$

† $0.01 < p > 0.001$

RESULTS

The results obtained from the 20 normal boys are listed in table 1 and the results obtained from the 20 normal girls are listed in table 2.

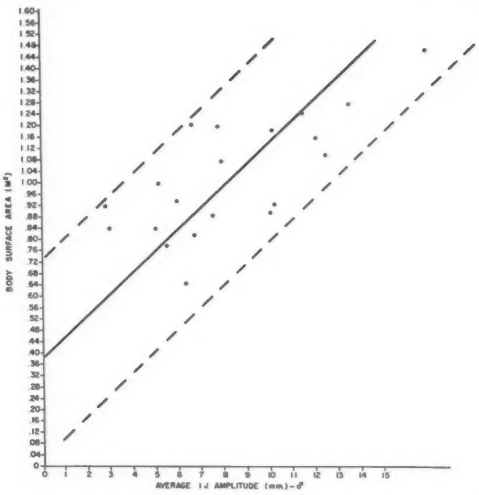

FIG. 1. The average IJ amplitude as measured from the ballistocardiograms of 20 normal boys are recorded as dots on the above graph. The solid line represents the predicted IJ amplitude and the broken lines represent the upper and lower fiducial limits at the 10 per cent level.

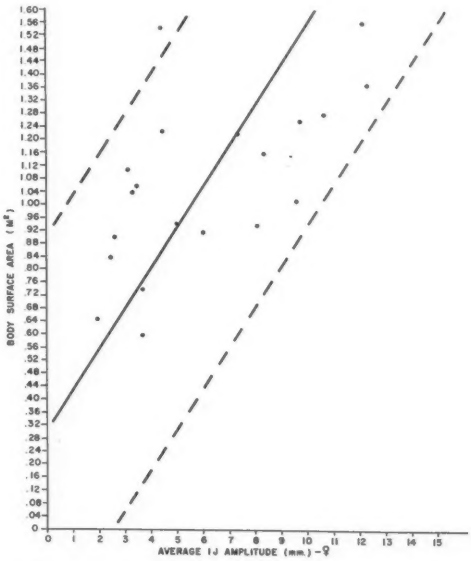

FIG. 2. The above graph represents the IJ amplitude data as obtained from the 20 normal girls and is recorded in the same fashion as in figure 1.

The results of the t test for evaluating the regression of average IJ amplitude on body surface area for both groups are tabulated in table 3. It is to be noted that a highly significant

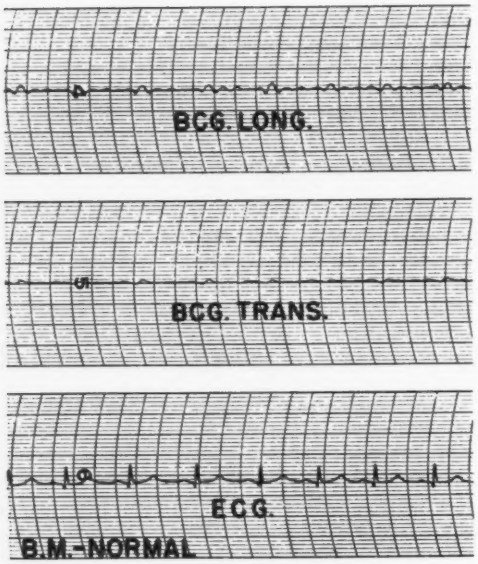

FIG. 3. B. M. is a 4 year old girl with a body surface area of 0.65 square meters. The wave pattern is normal, and the low amplitude of the ballistic waves is in accord with the subjects small body size.

correlation exists between average IJ amplitude and body surface area. The observed cardiac force as listed in tables 1 and 2 is equal to approximately twice the average IJ amplitude and would correlate similarly to body surface area.

Regression equations were used to determine the predicted average IJ amplitude. The results are seen in figures 1 and 2.

DISCUSSION

Scarborough's[6] study of 165 normal men and 77 normal women demonstrated a significant difference in IJ amplitude (mean, inspiratory and expiratory) of the men and of the women. It has been assumed that this difference in IJ amplitude is a result of the difference in body size. Considering the two groups separately, Scarborough was not able to demonstrate a correlation between body surface area and IJ amplitude. Using data obtained from Starr on 100 normal subjects, Scarborough obtained results similar to those of his own study, concluding that surface area has little influence on IJ amplitude.

The results of our present study indicate a close relationship between body surface area and IJ amplitude. However, the data obtained from the two groups cannot be combined. The boys and girls with small surface areas have similar IJ amplitudes. Although the mean body surface areas for the two groups are nearly the same, being, respectively, 1.02 and 1.07, the mean IJ amplitude of the girls is 75 per cent that of the boys. With increase in surface area, the difference is progressively greater. Obviously, this difference is not a function of body size. We have no explanation for the difference in IJ amplitude of the two sexes, for with the same surface area, the heart mass and length of the great vessels should be similar.

The calculation of "cardiac force" requires fewer measurements than does determination of the mean IJ amplitude. If the respiratory variation is normal, the average IJ amplitude will be equal to approximately one-half the "cardiac force," as can be seen in tables 1 and 2. To reduce the number of measurements required, "cardiac force" may be calculated, divided by two and then substituted in figures 2 or 3 for comparison with the results obtained in our study. However, the results of our study are concerned with 40 cases, a number too small to be used as normal standards.

The results of our present ballistocardiographic study of 40 children together with the previous study of Morris and Braunstein[2] of 59 normal adults demonstrate that the IJ amplitude is related to body surface area and that the high-frequency ballistocardiogram distinguishes between large and small individuals.

As in adults, the wave pattern of the transverse ballistocardiogram varied from subject to subject. However, in all instances, it was of smaller amplitude than the amplitude of the longitudinal record. As we have previously suggested,[2, 7] the transverse ballistocardiogram appears to be of most value in the study of the abnormal record. It may be of particular value in the study of children with cardiac shunts.

Conclusion

1. There is a significant correlation between body surface area and IJ amplitude in normal children.

2. The two sexes must be considered separately, for the mean IJ amplitude of girls is less than that of boys. With increase in surface area, this difference is progressively greater.

Summario in Interlingua

Simultanee ballistocardiogrammas longitudinal e transverse esseva obtenite ab 20 normal pueros e 20 normal pueras de etates inter 4 e 15 annos. Esseva constatate que il existe un significativissime correlation inter le area del superficie corporee e le median amplitude basal IJ.

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CLINICAL PROGRESS

The Management of Hypertensive Cardiovascular Disease

By EDWARD MEILMAN, M.D.

A REMARKABLE variety of measures are effective in hypertensive disease including surgery, diet, drugs, and psychotherapy. Despite striking differences in their mechanism of action, these measures all have the ability to lower blood pressure. However, they are not simple to select and administer, nor are they successful in every case.

Except for rare instances, such as coarctation or pheochromocytoma, in which treatment can be directed at the specific cause of the hypertension, treatment remains empirical and largely a matter of trial and error. Nonetheless, such treatment is so effective in lowering blood pressure and alleviating many serious sequelae of hypertension that the outlook in hypertensive disease is more favorable than ever before.

The Advisability of Lowering Blood Pressure

The ease of measurement of arterial blood pressure has focused treatment and discussion, as well as the patient's anxiety, on the blood pressure level.

Objections to such treatment have included the beliefs that (1) it is the unaltered progression of vascular disease that kills and that lowering the blood pressure has no effect on this process[1] and (2) lowering the blood pressure may actually be harmful by depriving the tissues, beyond the constricted arterioles, of adequate nourishment. Support for the former comes from such examples as the progression of coronary disease, despite blood pressure fall after sympathectomy.

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When the blood pressure is lowered, however, a more typical picture is diminution of angina. The hypertensive patient with coronary disease or congestive failure whose blood pressure cannot be lowered is the one whose disease is likely to progress unfavorably. The second thesis, the occurrence of acute accidents such as myocardial infarcts or cerebral thrombosis after sudden severe hypotension, particularly from spinal anesthesia or ganglionic blockade, is understandable in view of the frequent coexistence of hypertension and vascular disease. This indicates the importance of lowering blood pressure cautiously and slowly in older patients and, when possible, with the least disturbance of important homeostatic mechanisms.

A strong brief for the role of persistent and marked blood pressure elevation in the pathogenesis of the vascular lesion of malignant hypertension is given by Pickering.[2] Yet it is clear that there is no necessary correlation between the blood pressure level and the degree of hypertensive cardiovascular disease. Clinical improvement need not coincide with blood pressure fall. In animals, vascular lesions resembling those of malignant hypertension occur without high blood pressure and, in man, progressive papilledema has been described despite lowered blood pressure.[3] These situations are exceptional, for most studies attempting to correlate blood pressure level and prognosis indicate that the higher the diastolic level the worse the long-range outlook.[4] Probably the most compelling evidence for measures aimed at lowering blood pressure comes from the experience with malignant hypertension.[5] In this condition, formerly almost uniformly fatal in months to a few years, drugs, diet,

surgery and fever have all induced remarkable remissions. The most recent data of Schroeder, Morrow and Perry[6] indicate not only a high salvage rate, with restoration of vision and rehabilitation of many individuals back to work, but the virtual elimination of congestive heart failure as a cause of death in patients whose blood pressure is lowered adequately.

In less severe forms of hypertensive disease, satisfactory treatment requires more than alleviation of symptoms and lowering of blood pressure. Decrease in heart size, lessening or disappearance of albuminuria and improvement of electrocardiogram and retinopathy should follow. Proof that hypotensive measures prolong life in less severe stages of hypertension will be more difficult to obtain, but it seems logical that therapy, effective in the most severe forms of an illness, ought to have some value in milder forms. For all hypertensive patients, but particularly the less severe ones, the risks and discomforts of hypotensive therapy must be weighed against the life expectancy.

Prognostic Factors

Common clinical experience agrees with published reports[7] that many hypertensive individuals live to advanced age and succumb to the same causes, mainly cancer, as persons with normal blood pressure. A "benign" course, that is, duration of life to within 3 or 4 years of the life expectancy, is indicated by 8 years of documented hypertension (at least 180/110), without evidence of cardiac, renal or severe fundal changes.[8] However, a considerable number of hypertensive patients, including many with "benign" hypertension, die of congestive failure, myocardial infarction, cerebral hemorrhage and, occasionally, of uremia. When death or hemiplegia occurs from hypertensive disease, it is frequently at relatively young ages and often without much warning or overt evidence of vascular disease.

There is general consensus that "benign" disease is common in the female, especially beginning postmenopause and, conversely, the prognosis is poorer in males, especially young ones. The disease appears to be more severe and more difficult to treat in the Negro.

Determination of the prognosis for a single patient, except in the malignant phase, is difficult, even when early evidences of hypertensive disease, as grade II fundi, left ventricular hypertrophy or 1+ albuminuria, are present. Early morning headache may be present for many years without evidence of deterioration, but sudden onset of violent headache is an ominous symptom.

The blood pressure level, especially office readings, should be interpreted more leniently, particularly in view of revised (and higher) values[9] of "normal" blood pressure with increasing age; but sustained high diastolic pressure, 130 or more, is an unfavorable sign. Office readings, especially casual ones, are notoriously poor guides to the level of hypertensive disease or to the effectiveness of therapy. As pointed out many years ago and repeated recently, home blood pressure readings are more reliable.

The prognosis for the individual must vary depending on the underlying disturbances (renal, endocrine, atherosclerosis, neurogenic, "essential") that result in or are accompanied by hypertension. Subdivision of hypertension into types and in terms of response to specific hypotensive measures may eventually be helpful in this regard. Prognosis is certainly related to the family history as well as the presence and, more particularly, the rate of progression of vascular disease. An estimate of the latter requires prolonged observation. During this time, baseline studies are made, specific etiology for the hypertension is sought, good doctor-patient relationship established and, when indicated, hypotensive therapy is initiated. Examination of the eyes, the heart, and the kidneys reveals whether the patient is tolerating his elevated blood pressure with impunity. Hemorrhages and exudates in the fundi, an enlarging heart and progressive electrocardiographic changes of left ventricular hypertrophy and the appearance and persistence of albuminuria are indications that the process is not altogether benign. Difficulties in prognosis should not, however, result in allowing irreversible stages of the disease to develop while estimating the rate of progression.

As success in treating hypertensive disease

increases, life expectancy for the individual will increase. This is already apparent in the improved outlook for malignant hypertension. Congestive failure, formerly a common cause of death in hypertension, is now so amenable to hypotensive therapy that death from this cause is quite infrequent. However, there is not yet clear evidence that cerebral thrombosis or hemorrhage is postponed or prevented.

Choice of Treatment

The multiplicity of therapeutic measures in hypertension indicates that none is ideal. However, each has specific indications and when properly used, often in combination, can modify many of the sequelae of hypertension. Current therapy includes: (1) psychotherapy, (2) diet, (3) drugs, and (4) surgery. Fever therapy is of historic interest only.

1. *Psychotherapy*

Much of the effect on symptoms and blood pressure level, formerly attributed to drugs, diet, and surgery, is due to the psychodynamics of the doctor-patient relationship. When this relationship is used wisely by the physician, it can become an important adjunct in therapy. In fact it is important even when the physician and patient are unaware of it.[10] The patient must find stability, reassurance and protection in this relationship as well as a reorientation of his way of life. He must be taught to recognize the stresses that constrict his vessels and raise his blood pressure. He should be assured that his condition is benign and that casual blood pressure levels lack significance. He should be made to believe that he will not be paralyzed by a stroke—one of the most common and disabling fears of the hypertensive patient. He should be told that he has hypertension and that treatment is available, if necessary, but that frequently no specific treatment is required. For such assurance to be effective the physician himself must be free of anxiety about the disease and its treatment.

Some hypertensive patients have personality defects that antedate the development of persistent hypertension. These patients have a facade of affability and tolerance to situations, but actually they handle latent hostility poorly; they develop and sustain feelings of anger without expressing it. They have overanxious reactions to real-life problems. Severe emotional stresses often coincide with the onset of hypertension or with acute episodes in the disease. Malignant hypertension commonly has its onset with severe emotional duress.

Psychiatric treatment directed at the personality defects and the individual's response to stresses is relatively new as a treatment in hypertensive disease. Some dramatic results in early hypertension and in a few cases of severe hypertensive disease are reported; but it is too soon to state whether intensive psychotherapy, even if practical, will be productive of maintained improvement in advanced hypertensive disease. In these patients, precious time should not be lost by relying completely on psychotherapy.

Superficial psychotherapy, firm reassurance, reorientation of the patient's life to avoid unnecessary stresses and common-sense hygiene are all that is required in many cases of high blood pressure, particularly early or labile hypertensive people without evidence of vascular disease. Mild sedatives (phenobarbital and bromide) are recommended, although there is no evidence that they exert a salutary effect on the prognosis. In some instances (see below), other drugs are advisable for the labile patient in addition to psychotherapy.

2. *Diet*

Dietary management for hypertensive disease should hold a more important place than it does in this pharmaceutic heyday. Weight reduction for the obese patient should be carried out for its own sake, for its effect on general good health rather than expectation of normal blood pressure.

The mainstay of the dietary treatment in hypertension is sodium restriction.[11] Of the various low-sodium diets the rice diet[12] has the lowest sodium content (it is also the lowest in fat, cholesterol and protein). The claims of its original proponent concerning efficacy have been confirmed by others.[13] Improvement may be expected in one fourth to one half of the patients treated. However, except in very

rigid or obsessive patients, adherence to the diet for prolonged periods is difficult. Demonstration of its effectiveness in restoring lost vision, for instance, will enable some patients to remain on the diet for long periods. For most individuals the greatest usefulness of the rice diet lies in creating ready acceptance of a 200-mg. sodium diet. As long as the sodium content is not raised above 500 mg. per day, the hypotensive effects are maintained even if fat and protein are added. There appears to be no advantage of the rice diet over a 200-mg. low-sodium diet. Because most low-sodium diets are low in protein, there is an initial loss of weight but eventual stability. For patients with heart failure or malignant hypertension, as well as uncomplicated hypertension, sodium restriction alone is often effective. In patients with cerebrovascular disease, it is undoubtedly the safest.

It is helpful to establish the patient's response to salt restriction before instituting hypotensive drugs because low-sodium diets have an additive and possibly synergistic effect with some of these drugs. Certainly the hypotension resulting from ganglionic blockade is potentiated and it may be necessary to restore some salt to the diet to avoid excessive hypotension.

On this diet, even with initially normal kidney function, a low-sodium syndrome characterized by weakness, nausea, vomiting and collapse may develop in some patients. This is more likely in the presence of renal disease; yet some individuals with a moderate degree of nitrogen retention will show marked improvement on the rice diet. Curiously enough, the commonest complication noted on the rice diet was exacerbation of symptoms of peptic ulcer. As yet there are no reports involving combination treatment of low-sodium diet and Rauwolfia, but this ought to be a safe and effective program.

The rigors of sodium restriction make it obvious that it should be used only in patients with severe degrees of hypertension or with evidence of vascular disease such as grade III or IV eyegrounds, enlarged heart with congestive failure or coronary artery disease, or early renal disease. The only contraindication is a significant degree of renal failure.

3. *Drugs*

Although there are some criteria for the selection of particular hypotensive drugs, only a trial can demonstrate whether a given drug will be effective in a specific case.

A. *Rauwolfia serpentina.* The newest and most intriguing of the hypotensive drugs comes from *R. serpentina.* This ancient medicament from India was introduced into the United States by Wilkins[13] a few years ago and has already had intensive trial and study.[14] More recently it has been applied to a wide variety of psychiatric disorders. The crude root, standardized alkaloidal extracts and the pure alkaloid, reserpine, all seem to have similar pharmacologic properties, except that reserpine is about 100 times as potent as the crude root. An almost flat dose-response curve, unique among hypotensive drugs, gives reserpine a remarkable degree of safety. Children who have ingested very large amounts of the drug have suffered only from excessive sedation and diarrhea. Rauwolfia acts on the central nervous system, presumably at the hypothalamus and its ability to decrease blood pressure and heart rate has been attributed to a central inhibition of sympathetic (or an enhancement of parasympathetic) activity. The vasodilatation resulting in the blood pressure fall is mediated over sympathetic nerves to the vessels, apparently as a result of inhibition of reflex sympathetic vasoconstriction. However, postural hypotension does not occur except in very rare instances. Pupillary constriction is a characteristic effect in animals and nasal stuffiness in man. The latter may result in symptoms of a chronic cold, bloody nasal discharge and even sinusitis and otitis. Further evidence of parasympathomimetic activity is the increased secretion of hydrochloric acid in the stomach which could potentially exacerbate peptic ulcer; increased intestinal motility may result in diarrhea. In addition, Rauwolfia, like the Veratrum esters, interferes with certain reflex blood pressure rises, mediated by the central nervous system, that are the

normal response to anoxia or carotid sinus occlusion.*

Decreased motor activity in animals and placidity in man are effects that may indicate more complicated central nervous system action. The peculiar kind of sedation induced by reserpine has been aptly called "tranquillity," but this change in personality passes readily from calmness and quietude to languor and even true depression. The latter is more likely with excessive doses, but has also occurred with doses in the usual clinical range. Nightmares of a violent nature may occur but these are usually transitory. Decreased libido in the male is not uncommon. A few cases clinically like paralysis agitans have appeared under treatment with Rauwolfia, but these are apparently quite rare and usually related to excessive dosage. Emphasis on these side actions should not detract from the safety and remarkable therapeutic effects of these drugs. In general, Rauwolfia has only a moderate hypotensive activity and is said to be most successful in young, labile hypertensive persons without vascular disease. Yet often a marked and gratifying blood pressure fall is observed in elderly persons with "fixed" severe hypertension and definite evidence of hypertensive cardiovascular disease. The hypertensive personality described above is altered. The patients seem better able to withstand many emotional stimuli. Anxiety is diminished. The tachycardia, blood pressure rise and "diencephalic" facial flushing (with which some hypertensive women greet their doctor) or other stresses disappear under treatment with Rauwolfia. Many of the so-called neurotic symptoms such as dizziness, headache, nervousness and insomnia are relieved. Some blood pressure diminution is noted in about one half of the patients treated.

The dose range of reserpine is 0.1–1.0 mg. daily by mouth, the average being about 0.25–0.5 mg. The drug is best taken at night. Parenteral reserpine (1–2.5 mg. intravenously) has in general the same effect, predominantly sedation and a moderate blood pressure fall lasting about six hours. Neither tolerance nor addiction has been reported. Best effects may require one to several weeks of treatment; similarly, when the drug is omitted hypotensive effects may last for weeks. Undesirable side effects are often controlled by omitting the drug for 1 week in 4. If daytime sedation is excessive, the entire dose should be taken at night. Synergistic effects with other hypotensive drugs are always difficult to prove, but the hypotensive effect of Rauwolfia is at least additive to other hypotensive drugs. The resulting bradycardia tends to overcome the acceleration of the heart induced by hydralazine; its bowel-stimulating action may moderate the constipation from ganglionic block; its tranquillizing effects seem to make Veratrum effective with less vomiting. Smaller doses of the other hypotensive drugs are required if the patient is receiving Rauwolfia.

R. serpentina, therefore, seems to be a worthwhile drug in early, mild cases, especially if nervousness or tachycardia is prominent and psychotherapy is ineffective. In more severe cases, with headache, dizziness, or evidences of hypertensive cardiovascular disease, it may be useful alone but more likely in combination with other drugs. As Wilkins has stated, it should be the first (hypotensive) drug tried and the last omitted. No deaths have been reported from its use and even the severe side effects, such as depression, yield to withdrawal of the drug.

B. *Veratrum Alkaloids.* The Veratrum alkaloid esters are another group of hypotensive agents obtained from plants. Both hypotensive and side effects are similar whether one uses crude root, standardized alkaloidal extract, or purified derivatives such as protoveratrine A and B. In view of the narrow range between therapeutic and toxic doses (approximately 30 per cent) pure substances administered by weight are more desirable than biologically standardized material.

Study of the pharmacologic action of these drugs has revealed the existence of a reflex causing a fall in blood pressure and heart

* Reserpine causes increased excretion of 5-hydroxy-indole acetic acid, a metabolite of serotonin, in dogs and the discharge of large amounts of serotonin from the small intestine of rabbits.[35] Serotonin is capable of activating the coronary chemoreceptor reflex.[16]

rate from afferent stimulation of chemical receptors in the heart and great vessels (the Bezold-Jarisch reflex).[15]

The Veratrum esters elicit a veratrinic response (repetitive electric discharges from a single stimulus) in the chemoreceptors of the carotid sinus and coronary vessels. Increased afferent electric activity is transmitted via the carotid sinus and the vagus nerves to the central nervous system, which in turn causes a diminution in efferent electric activity over the splanchnic[16] and presumably other sympathetic nerves. Hence, vasodilation and fall in blood pressure occur. Accompanying and increasing the hypotension is a bradycardia due to increased reflex vagal activity. A stimulating effect on the nodose ganglion in cats seems to be the source of the vomiting reflex. Toxic doses of the drug in man cause epigastric and substernal oppression, nausea, vomiting, sweating, marked hypotension, bradycardia, and even heart block or extrasystoles. The disturbances in rate or rhythm are vagal phenomena and are readily overcome by atropine (0.5–1.0 mg. subcutaneously or intravenously). Ephedrine sulfate (25–35 mg. subcutaneously) or other vasoconstrictor drugs counteract an excessive blood pressure fall. At the height of the hypotensive reaction there may be transient electrocardiographic changes such as T-wave inversion in V_3 and V_4. These changes are reversed by atropine, but not by oxygen, indicating that they are due to vagal stimulation rather than to anoxia. There is no paralysis of autonomic activity and consequently interference with postural reflexes does not occur. However, if a toxic dose causing marked hypotension has been given, standing may cause a further fall in blood pressure. Cardiac irregularities are more likely in patients receiving digitalis or quinidine. Oliguria may occur during the hypotension from Veratrum, resembling that seen after any sudden fall in blood pressure, but it is transitory and not accompanied by fluid retention. Renal function is not adversely affected unless uremia is present.[17] However, in some patients with nitrogen retention cautious lowering of the blood pressure may be achieved without much aggravation of the renal status. Once frank uremia is reached, any hypotensive measure will aggravate the renal insufficiency, but control of encephalopathy, headache, diminishing vision, and heart failure may be obtained.

Although there is a narrow range between the hypotensive and toxic or emetic dose, these alkaloids, particularly protoveratrine,[18] can be given intravenously with only rare toxic effects. Vomiting is more likely to occur with subcutaneous or intramuscular administration and is even more common with oral drug therapy. Protoveratrine can be given intravenously with predictable results if dosage is based on the patient's weight. The initial dose should be 1.5–1.9 μg. per Kg. followed by 20 μg. every 10 minutes until the blood pressure is satisfactorily lowered. Subcutaneous or intramuscular dosage is 4 to 6 μg. per Kg. given at 6 to 8 hour intervals. Parenteral administration may be compared to digitalization with a rapidly acting digitalis glycoside. Prolonged parenteral and oral administration presents the problem of increased incidence of vomiting, which limits the usefulness of this drug in treating chronic hypertensive disease to not more than one fourth of the patients. In this latter group the drug may be given for long periods without loss of responsiveness and only occasional episodes of nausea and vomiting. Because of the side effects, oral drug administration requires close supervision of dosage, usually with 3 or 4 daily doses i.e., a half hour after breakfast, at about 2 p.m., a half hour after supper and at bedtime. The dose must be worked out by trial, and an average initial program would be 0.5 mg., 0.25 mg., 0.5 mg., 0.25 mg. in 4 daily doses as above. Increments should be 0.125 mg. only. Hoobler and coworkers[19] have recommended 1 large dose (0.5 to 1.5 mg.) after breakfast followed by 2 small doses (about 0.25 mg. each) at 2 to 3 hour intervals; a similar program starting after supper has been helpful in controlling nocturnal dyspnea.

The Veratrum alkaloids are probably the drugs of choice when prompt predictable fall in blood pressure without elevation of cardiac output or disturbance in homeostatic reflexes is desired. They are virtually specific in cases of pulmonary edema associated with acute

glomerulonephritis, hypertensive encephalopathy, the hypertension and convulsions of toxemia, and cortisone-induced hypertension. They may be a useful adjunct in the treatment of hypertensive congestive failure and are very useful in malignant hypertension with early or threatening loss of vision. In these instances the parenteral route should be employed. Of 9 patients with malignant hypertension treated with parenteral protoveratrine, 5 had remissions and were alive 1 to 3 years later.[20]

Patients with congestive failure or coronary disease complicating hypertension who show a satisfactory hypotensive response to Veratrum alone or combined with reserpine will have alleviation of failure and decrease in angina. Despite the acute nature of the toxic effects and occasional marked hypotension, no deaths are known to have occurred from its use. It is probably the best drug for parenteral administration for short-term therapy of acute hypertensive states. Its mechanism of action would make it the ideal drug were it not for its tendency to cause vomiting.

C. *Hydralazine.* Hydralazine (1-hydrazinophthalazine, Apresoline) is a synthetic agent whose hypotensive properties were described only a few years ago.[21] It is effective when given by mouth and appears to act on the central nervous system as well as against a number of circulating vasopressor substances. In animals, hydralazine exhibits sympatholytic activity, but in the doses used in man these effects are minimal. A marked increase in renal blood flow accompanies the moderate fall in systolic and diastolic pressure, yet it is not more effective in renal hypertension than in other varieties. It does not increase glomerular filtration rate and does not elevate to normal the depressed renal blood flow of essential hypertension.

A direct stimulating effect on the heart results in tachycardia and increased cardiac output, which explains the aggravation of angina pectoris and congestive heart failure often seen, even at lowered blood pressures. Although hydralazine may cause electrocardiographic changes of anoxia in patients with coronary disease, it is said to improve the contours of the ballistocardiogram, presumably because of peripheral vasodilatation. Rauwolfia or Veratrum should be used to slow the heart rate before hydralazine is given to patients with coronary disease or congestive failure. Some of the adverse cardiac effects of hydralazine may also be avoided if ganglionic-blocking drugs are used first.

Initial toxic symptoms include nausea, vomiting, some degree of postural hypotension, and headache. The last mentioned is common and often very severe but may be alleviated by antihistamine or analgesic agents. These symptoms usually subside in a few weeks and can be minimized by starting treatment with small doses. Continued administration has resulted in familiar types of drug reactions (fever, edema, rashes) and also a new type of drug reaction,[22] a collagen-like disease that has appeared in 8 to 10 per cent of patients receiving large doses for a year. This syndrome may include arthritis, rash, fever, anemia, hematuria, enlarged lymph nodes and spleen, albuminuria, positive cephalin flocculation, and even "L.E." cells. It has appeared mainly in patients who have received large doses that effectively lowered their blood pressure. Thus far, apparently, even when "L.E." cells are present, the syndrome has disappeared when the drug was omitted and, in some cases, corticotrophin given.

Initial dose should be 25 mg. or less four times daily. Increments of 25 mg. per dose are added every 3 to 4 days unless severe headache appears. Maximum daily doses have ranged from 500 to 800 mg. a day. In view of the high incidence of drug toxicity it is doubtful whether more than 400 mg. a day should be given. If hydralazine is used alone, prolonged administration is not only accompanied by a rising incidence of drug toxicity, but a diminution in the number of good responses. Initially satisfactory hypotension is obtained in about one third of the cases, but after 1 to 2 years of treatment good results have diminished to one tenth. Milder forms of hypertensive disease may respond to small doses of hydralazine, especially in conjunction with Rauwolfia or Veratrum without a high incidence of toxic reactions. In general, large doses of hydralazine

should be reserved for patients with severe forms of hypertensive disease in whom other treatment is inadequate. In conjunction with hexamethonium, however, it has been a very effective agent in severe forms of hypertensive disease.[6]

D. *Ganglionic-Blocking Drugs.* Demonstration of the striking ganglionic-blocking action of tetraethyl ammonium ion (TEA) led to a search for related drugs suitable for use in hypertension. Extensive pharmacologic studies[23] have given a good picture of the action of these drugs. Hexamethonium, its new prototype pentolinium [pentamethylene-1:5-bis-N-(N-methylpyrrolidinium)], and other related methonium compounds exert their action by interfering with cholinergic transmission at the ganglionic synapse and not at preganglionic or postganglionic structures. There is no paralysis of the effector end organs and they remain capable of reacting to a suitable stimulus. For example, the arterioles will constrict with norepinephrine; the salivary gland will secrete and the bowel contract with cholinergic drugs.

Interference with sympathetic nervous activity causes orthostatic hypotension and compensatory tachycardia in almost all patients. Blood pools in the legs and splanchnic area unopposed by reflex sympathetic vasoconstriction. This may be so severe as to cause faintness or even collapse. The patient should sit or, better, lie flat when such symptoms appear. Some degree of postural hypotension is considered essential to successful management and therefore cannot be considered a side effect. Smaller doses are required for patients who are up and about than those in bed. Alcohol, a large meal, vigorous exercise, hot weather, low-salt intake, mercurial diuresis, all tend to potentiate orthostatic hypotension. Other evidences of interference with sympathetic activity are seen in the increased susceptibility to certain stresses such as anesthesia and hypoglycemia. Less anesthetic agent is necessary in patients whose sympathetic nervous system has been blocked by methonium compounds. Similarly, the usual adrenalin-like reaction to hypoglycemia does not occur, the patient merely passing quietly into hypoglycemic coma. Interference with sweating may result in elevations of body temperature during warm weather; yet failure of reflex skin vasoconstriction may cause shivering in cool weather. Interference with potency, more severe in the older age group, is troublesome, but is relieved temporarily by omitting a dose of the drug.

Blockade of parasympathetic activity causes additional undesirable effects. Blurred vision and intolerance of bright light often require tinted eyeglasses with increased correction. Dryness of the mouth from decreased salivation is annoying; lessened intestinal motility progressing to severe constipation and even ileus, and urinary retention in the male patient with prostatic hypertrophy may be serious. Toxic reactions with oral medication are more severe and more difficult to treat because the oral dose is about 20 times the parenteral dose. Constipation must be avoided, especially with oral administration, because it may result in massive absorption of the drug from the gut, with resulting severe toxicity such as profound hypotension and a complete paralytic ileus.* Irritant or saline cathartics should be used to insure daily bowel movement. Failure to have a daily bowel evacuation calls for omitting the drug. Deaths have occurred from paralytic ileus and from cerebral or coronary thrombosis secondary to severe hypotension.

In their mild form all these symptoms are responsive to oral cholinergic drugs, such as pilocarpine (5 mg.), prostigmine (15 to 30 mg.), and urethane of β-methyl choline (Urecholine) (5 to 20 mg.).

As with many other new pharmacologic agents, hexamethonium has apparently introduced a new disease. A severe fatal pulmonary fibrosis[24] has been reported in a small number of patients who received large doses of the drug. These patients show severe tachypnea and dyspnea, which is improved in the supine position. The syndrome is more common in the malignant phase of hypertension and in the Negro.

Pentolinium has the same actions and ill effects as hexamethonium. It is more potent on a milligram basis but has not demonstrated

* This reaction can be readily differentiated from mesenteric thrombosis because the pupils do not react to light and the skin is dry.

decisively greater freedom from side effects or margin of safety. Its duration of action is longer than hexamethonium, however, and this represents a distinct advantage in oral medication.[25]

Pentolinium is administered in doses of 20 mg. (of the bitartrate salt) after breakfast, in midafternoon, and at bedtime. The dose is increased by 20 mg. slowly every few days until faintness in the upright position occurs, at which time slight reduction in dose is made. Tolerance occurs readily, both by mouth and parenterally, and during initial phases of treatment the dose must be increased. Eventually a stable dose is reached, but frequent adjustment, even diminution in dosage, is not uncommon. The desired effect is a systolic pressure not lower than 120 in the erect position.[25] Some investigators recommend home blood pressure readings,[6, 26] to obviate the notoriously unreliable "office" reading and to adjust medication on the basis of these home readings. Smirk[25] believes that subjective faintness or lightheadedness in the erect position is a satisfactory guide to dosage. With pentolinium the three daily doses need not be equal; study of the blood pressure response may indicate the desirability of making the bedtime dose larger and the dose after breakfast smaller than the midafternoon dose. Education of the patient so that he understands the effects and side effects of the drug is essential to good control. Satisfactory levels of blood pressure may be reached in two thirds or more of patients; one third may have normotensive readings in the erect position. Recently, a new synthetic ganglionic-blocking drug, Meborylamine, has been introduced for study. It has a longer duration of action than pentolinium and is completely absorbed from the intestinal tract.

Contraindications to therapy with ganglionic-blocking agents include (1) uremia, which is always aggravated, (2) prostatic symptoms, (3) generalized and, especially, advanced cerebral arteriosclerosis, (4) recent (6 to 12 weeks) coronary or cerebral thrombosis, (5) pyloric stenosis and (6) lack of cooperation or poor intelligence of the patient.

Patients who exhibit the malignant phase of hypertension, congestive failure, or other evidences of severe hypertensive disease should be treated with ganglionic-blocking drugs, preferably in conjunction with Rauwolfia or hydralazine,[6] if simpler measures have been tried and are ineffective.

E. *Choice of Drug Combinations.* Combinations of hypotensive drugs appear to be more effective and better tolerated than any single one of the drugs available today.[27] The undesirable effects of some of these are mitigated, probably because smaller doses of each are necessary, and because some tend to overcome adverse effects of others. The more powerful drugs are more dangerous and they should be employed only when simpler measures have had adequate trial.

For the patient with mild, asymptomatic, early hypertension, but no evidence of cerebral, heart, or renal disease, psychotherapy and reorientation to the stresses of life are adequate therapy. For the patient with hypertension proved benign by its long duration, especially elderly persons with only moderate degrees of left ventricular enlargement or 1+ albuminuria, again only firm reassurance is necessary. If symptoms not responsive to psychotherapy or phenobarbital are present, Rauwolfia can be employed.

Patients who show sustained high diastolic pressure, especially men, or have evidence of progressive but not malignant hypertensive disease should receive hypotensive therapy. Rauwolfia should be tried first. Next, sodium restriction (200 to 500 mg.) should be added. Failure to respond to this regimen in 2 or 3 months is indication for use of Veratrum (or protoveratrine) and later, if necessary, ganglionic-blocking drugs.

Patients with hypertensive cerebrovascular disease may be given Rauwolfia, low-sodium diet, Veratrum or small doses of hydralazine, in that order. The use of these drugs for acute cerebral accidents, such as hemorrhage, is still experimental.

Hypertension and coronary artery disease may be treated with Rauwolfia, salt restriction and Veratrum. Ganglionic-blocking drugs cautiously administered to lower pressure gradually and not too far, with the addition of small amounts of hydralazine, may give remarkable relief.

The development of congestive failure, or the malignant phase of hypertension, unresponsive to salt restriction or Veratrum calls for the addition of ganglionic-blocking drugs, such as hexamethonium or pentolinium and hydralazine.

For acute hypertensive crises Veratrum (or protoveratrine) is the drug of choice. Intravenous sodium nitroprusside has been recommended recently.[28] Ganglionic-blocking drugs are also often effective, but not so easily controlled and less desirable in cases such as eclampsia, where anesthesia may be utilized or precipitous blood pressure falls are to be avoided.

One half or more of patients with malignant hypertension can now expect reversal of the accelerated phase of the disease, if uremia is absent,[5, 6] from combinations of drugs or surgery. All forms of therapy fail in hypertension, once uremia is present; but mild degrees of nitrogen retention occasionally respond dramatically to drugs or diet. Once these agents have induced a satisfactory hypotensive effect, it is important that therapy not be stopped abruptly, especially in patients with malignant hypertension, lest uremia, cerebral hemorrhage, or heart failure be precipitated.

4. *Surgery*

Unfortunately, treatment with drugs or diet is not always effective in hypertensive disease. For some severely ill patients, it may be desirable to recommend surgery. No patient should have a sympathectomy or adrenalectomy without a prior trial of drugs, including ganglionic-blocking agents.

After more than two decades of experience with resection of portions of the sympathetic nervous system for hypertension, popularity for this procedure seems to be declining. This is primarily because there is still no agreement on the best operation nor are there valid criteria to indicate which patients are likely to benefit by the operation.[29, 30] In a careful study, Hoobler and co-workers[31] were unable to indicate any clinical differences between patients who did well after sympathectomy and those who did not. In addition, prolonged morbidity may follow the operation. Although surgeons claim that one half of their patients are helped by this procedure, most medical men feel that the maximum figure is one third and many believe it is no more than one tenth. Sympathectomy was clearly the first procedure, however, to alter the poor prognosis in malignant hypertension. There is not yet agreement that life expectancy in milder degrees of hypertensive disease is increased. Lack of knowledge of the life history of untreated cases and the difficulties in prognosticating for the individual patient, make it as difficult to evaluate results of sympathectomy as of other treatment programs.

The variety of surgical procedures recommended has extended to virtually total sympathectomy. This last procedure represents formidable and multiple surgery, and most surgeons do not believe it offers more than the less extensive operations. The most widely used surgical procedures are those of Peet[32] and of Smithwick.[33] The former is often done in one stage; it does not entail prolonged morbidity from postural hypotension and does not interfere with ejaculation. The sympathetic chain, from the sixth to the twelfth thoracic, including the splanchnic nerves, is resected on both sides. Portions of two ribs must be removed and the operative mortality is three per cent. The Smithwick procedure includes the lumbar ganglia, thus resulting in postural hypotension and interference with potency. This procedure has the advantage of exposing the adrenal glands, to detect a rare instance of pheochromocytoma, as well as the kidneys. Both procedures may cause severe persistent postoperative neuritis. There is disagreement concerning the necessity of postural hypotension for a good therapeutic response with improvement in survival rates. Kahn[29] found no significant difference between the survival rates in Peet's and Smithwick's series; yet one of the alleged requirements for good result with "medical sympathectomy" is some degree of postural hypotension. Lowered blood pressure should persist for a year before the operation can be considered successful.[31]

While the exact role of sympathetic surgery remains unsettled, having been displaced to a large extent by ganglionic-blocking drugs, there

are a few situations in which operation should be recommended. Any patient with malignant hypertension not responsive to medical treatment within a reasonable period (e.g., 2 to 3 months) should have sympathectomy if nitrogen retention is absent. Surgery is invariably unsuccessful when nitrogen retention is present. Sympathectomy should be advised for patients with evidence of rapidly progressive but not necessarily malignant phase of hypertension who cannot be followed very closely, live far from good medical attention, and lack the intelligence and cooperation necessary in using the more potent hypotensive drugs or have not responded to medical treatment. Apparently sympathectomy increases the effectiveness of drugs and diet.

Adrenalectomy, with or without accompanying splanchnic resection, is at present an experimental procedure.[34] The good results reported can often be equaled by sympathectomy alone or with sodium restriction. In such patients, strict low-sodium intake, with additional measures if necessary to cause negative sodium balance (mercury, resins), and ganglionic-blocking drugs should be equally effective. Patients whose adrenal glands are removed face the life-long likelihood of acute serious illness with infection, stress, or omission of cortisone. Moreover, some patients may show simultaneously high blood pressure and the serum chemical derangements of adrenal insufficiency, not to mention the hazards of cortisone psychosis and metabolic accidents.

From the empirical and varied nature of the treatment outlined above management in hypertensive disease is obviously far from ideal. The physician's problem is complicated by (1) lack of uniform classification of hypertension in terms of etiology, severity and complicating vascular disease; (2) inadequate data on life history and inability to prognosticate for the individual case; (3) lack of agreement concerning indications for treatment, choice of treatment and the results of treatment and (4) the dangers and discomfort of this therapy. Nonetheless, with proper exercise of his science and art, always bearing in mind *non nocere*, the physician can do more for hypertensive patients than ever before. Measures successful in lowering blood pressure will alleviate, and possibly prevent, many of the serious sequelae of this disorder.

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Auscultatory Diagnosis of Valvular Heart Disease

By GEORGE DAVID GECKELER, M.D.

THE impact of cardiac surgery has led to increasing interest in the auscultatory diagnosis of valvular heart disease; many physicians have come to realize that they might benefit from a better understanding of this subject. During the past century a remarkable amount of usable knowledge has accumulated in spite of the imperfections of this art, the limitations of human hearing in the low range of sound and the inadequacy of the stethoscope as an acoustic instrument. In recent years, training of the younger man in this art has been deficient with the greater interest in electrocardiographic, radiologic and other graphic methods during his training period. One is frequently asked what constitutes the best stethoscope. I have had great satisfaction with a Bowles chestpiece 2 inches in diameter instead of the usual one and one-half inches; the larger size amplifies low frequency sounds and for many is a distinct advantage. Even with the ideal stethoscope, there is, of course, no substitute for self discipline, persistent training and knowledge of what is normal.

A good technic is imperative for listening to auscultatory findings. There is a great tendency to place the chestpiece of a stethoscope at some auscultatory area and simply to listen; but this is poor practice. To develop proficiency in this field one must learn what to listen for and to listen for just one thing at a time; one must learn not to listen to heart murmurs, while listening for the characteristic features of heart sounds. All auscultatory phenomena must be analyzed for their pitch, loudness and length. During intent listening it is helpful to eliminate all other sensory stimuli as much as possible by being comfortable and closing the eyes. In the future, electronic means will certainly be used for recording and reproducing heart sounds and murmurs. Instead of 5 or 6 students grouped around a patient's bed for a 50 or 60 second period of listening, an instructor may use a microphone, amplifier and speaker, with or without tape recordings, to large groups of students with repeated presentations of many different abnormalities. The time allotted is utilized much better in this way and patient fatigue is eliminated. Furthermore, with tape recordings an abnormality can be compared with normal heart sounds or with another abnormality, an example can be slowed and murmurs from heart sounds can be dissected. Regardless of what technic is used, however, an examination should always be done in a methodical manner: the examiner should subject himself every time to a specific routine, first considering disturbances of rate and rhythm, then listening in various areas for heart sounds and then for murmurs or adventitious sounds.

The value of auscultation is probably greater in rheumatic valvular disease than in any other type of heart disease. In the acute rheumatic state, disturbances of rhythm, and particularly a gallop, may be very significant. A diastolic gallop rhythm, with a rhythmic lilt of three sounds and the abnormal third sound in diastole, simulates the pronunciation of the word "Tennessee" and usually can be differentiated from other three-sound cycles without much difficulty. Premature beats warrant further investigation; if they are of atrial origin and increase in frequency, they may be the precursor of a serious disturbance. Sinus rhythm or sinus tachycardia is the usual find-

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ing, however. When the active process subsides in a child, sinus arrhythmia very often develops. Heart sounds are not characteristically changed, except for some reduced intensity, and murmurs are not significantly different from those found in the inactive state. Adventitious sounds, such as a pericardial or even a pleural friction rub, must be anticipated and looked for carefully. The high-pitched scratch of a friction rub, sometimes heard only during systole and later developing during both phases of the cardiac cycle, may be very transient and disappear with effusion; then the sounds at the apex gradually become fainter and they may even become inaudible.

Mitral Valvular Disease

In the inactive state valvular damage is the only significant abnormality that may be appraised by auscultation. Because the damage is related in such a large proportion of cases to the mitral valve alone or in combination with other valve lesions, meticulous care should be used to determine whether this valve has been damaged and, if so, to what degree it has been deformed. The first evidence of damage is a mild degree of insufficiency caused by distortion of one or both of the leaflets, possibly associated with shortening of the chordae tendineae. This slight insufficiency results in heart sounds at the apex that may be normal or replaced partially by a systolic murmur, either rough, blowing or musical in character. In children, this mild-degree rheumatic insufficiency may be difficult to distinguish from an innocent murmur. At least 50 per cent of patients with rheumatic heart damage do not give a history of any etiologic factor, even after a careful investigation, so that a negative rheumatic history is not helpful. An innocent murmur must be systolic in time, blowing in character, and not more than grade 1 at the apex or grade 2 at the base. Associated with it there must be no other abnormal auscultatory finding, no electrocardiographic or radiologic evidence of heart disease and no past history of illness that might cause heart disease.

With further deformity of the mitral leaflets, stenosis begins to appear. First there is a wide reduplication of the mitral second sound (an opening snap), which is quite characteristic. Usually it is heard at or near the apex; often it is just inside or outside the point of maximal impulse. It is quite different in character from the usual, reduplicated mitral first sound or aortic or pulmonic second sound. It is often associated with a systolic murmur. If the degree of stenosis increases, the second part of the reduplicated mitral second sound trails off as a short blowing mid-diastolic murmur; as a rule this murmur is very difficult to hear and it is necessary to turn the patient (usually a child) to the left lateral position. The murmur is best heard at the apex as a heart returns to its normal rate after slight exercise; it is often not heard when the heart is quiet. Usually the first sound is not sharp at this stage. Recognition of this minimal deformity is particularly important in view of the present-day prophylactic regimen for the rheumatic child and the warrantable hope that with sincere parent cooperation further damage may be avoided. If a further degree of stenosis develops, the first sound becomes definitely sharp and with it is heard a presystolic accentuation of a mid-diastolic or late diastolic murmur; as a rule, this occurs only after childhood. If congestive heart failure intervenes, the presystolic murmur may become much less prominent or disappear altogether for a time; however, the sharp first sound persists even though its intensity may diminish. Until recently it has often been taught that this sharp first sound is loud; its characteristic features, however, are its pitch and duration, which are higher and longer than normal. There has been considerable argument whether the presystolic accentuation of the murmur of mitral stenosis had crescendo accentuation. In recent spectrograms about half the murmurs show a gradually increasing rise in pitch as the murmur progresses to the first sound. Usually there is no systolic murmur at this stage; the presence of an associated regurgitant effect is still undetermined. Severe stenosis of the mitral orifice and fixation of the leaflets would seem a priori to necessitate regurgitation; when the leaflets of postmortem specimens are fused and fixed in this degree of stenosis, there always appears to be some degree of associated insufficiency. With the twist-

ing action of ventricular systole, however, there may be no insufficiency, for the dynamic effect may be very different from the static appearance. Very rarely the presystolic murmur of advanced mitral stenosis is heard with a tumor in the left atrium. Inconstancy of the murmur with change of position of the patient, however, makes one suspicious of such a tumor.

With calcification of the valve leaflets, increase in age and incipient congestive heart failure, atrial fibrillation replaces the sinus rhythm and usually, but not always, the crescendo effect of the mid-diastolic or late diastolic murmur disappears. The sharp mitral first sound may persist, but it may be overshadowed or replaced by the systolic murmur of associated insufficiency. With increased pressure in the pulmonic circuit of long duration, the pulmonic second sound becomes louder. It is not known whether the loud second sound is the result of change in the diameter and length of the pulmonary artery, in the size of the right ventricle compared to the pulmonary artery or in both. For several weeks after a successful mitral commissurotomy with reduction of a very high preoperative pulmonary artery pressure to normal, the pulmonic second sound is as loud as before operation. These findings were confirmed by tape recordings with an identical technic before and after operation. In many older adults, the loud pulmonic second sound persists for a long period of time. Probably as the result of right ventricular and pulmonary artery enlargement, the pulmonic second sound is heard lower than the second right interspace, very frequently as low as the fourth left interspace. Because of its loudness, the pulmonic second sound is widely transmitted and may overshadow the second sound at the apex, at times causing the second sound at the apex to be louder than the first sound. Many times it is reduplicated, but this effect is not significant; the degree of loudness is the important feature.

In a few instances, of course, the major mechanical deformity may not be narrowing but a widening of the mitral ring with a severe grade of insufficiency associated with scarred and shortened chordae tendineae. There the mitral first sound is partially or entirely replaced by a systolic murmur. As a rule the murmur is rough and loud, but with very advanced insufficiency there actually may be no murmur at all. These patients show unusual incapacity and left ventricular enlargement in addition to their severe left atrial and right ventricular damage. While both mitral stenosis and mitral insufficiency can be helped by surgery, one must decide whether the degree of insufficiency in a mitral stenotic valve contraindicates surgical intervention. Auscultation is helpful, but in the last analysis the size of the cardiac chambers, particularly of the left ventricle, and the functional status of the heart are decisive.

Aortic Valvular Disease

The diagnosis of rheumatic aortic valvular stenosis usually can be made by auscultation. Both the second right and the third left interspaces near the sternal border should be regarded as aortic areas where sounds and murmurs from the aortic valve may be transmitted. If acquired aortic stenosis is present, a rough systolic murmur is heard in these areas associated with a diminished or absent second sound or with an early diastolic murmur, if there is associated aortic insufficiency. The systolic murmur is invariably rough but is of different pitch than the murmur caused by the mitral insufficiency. This rough murmur is usually transmitted, if it is loud, but transmission is not specific; in large part it depends upon the structure through which the sound travels. With associated severe mitral damage, the pulmonic second sound may be accentuated and may be heard along the left sternal border at the fourth or third interspace. Fortunately, transmission of this loud second sound usually is not to the right and the intensity of the second sound in the second right interspace usually is related to aortic valve function. Comparison of the aortic and pulmonic second sounds is not helpful; it is much more dependable to compare the degree of loudness of this aortic second sound with what one would expect at a certain age. The vascular effects of aortic stenosis of low systolic and reduced pulse pressure depend upon the degree of stenosis; if surgery is contemplated, the degree of stenosis should be determined more accurately

by electrocardiograms, roentgenograms and arterial pressure curves. A thrill may also result from aortic stenosis but its absence should not militate against a diagnosis of this lesion. Subaortic stenosis of congenital origin may be suspected when a normal or loud second sound is heard with the other findings of aortic stenosis. At times this differentiation is difficult; but it should be made, if at all possible, because the operative procedures differ for the two conditions.

Aortic Insufficiency

While syphilitic aortic insufficiency is still seen, rheumatic disease is the preponderant cause. As in aortic stenosis, varying degrees of insufficiency give rise to the auscultatory findings with or without the vascular findings. With maximal intensity in the second right or third left interspaces, the diastolic murmur invariably is heard immediately after or in place of the second sound. While this murmur is almost always blowing in character, long-standing rheumatic involvement with sclerotic change of the valve leaflets may cause a rough early diastolic murmur to be heard. If calcification is considerable, it may be inferred that the leaflets are nonflexible; any surgical attempt at correction of the valve may not help and may accentuate the valvular deficiency. Determination of amount of calcification may be very difficult; as in aortic stenosis, more definitive studies must be carried out prior to surgery for this purpose. Occasionally, the early diastolic murmur of aortic insufficiency is not maximal in intensity at the base, but for some unexplained reason only near the apex, and at times well out into the lower left axillary region. As a rule this is only temporary, often during acute carditis or with severe failure; with recovery the murmur disappears from these areas and reappears at the base. Transmission of the murmur depends upon its loudness and the structures through which it must pass. In contrast to the murmur of mitral stenosis, it very often is heard over a large area of the precordium. If the patient leans forward in the sitting position after slight exercise, this murmur is usually more clearly audible. At times with a severe grade of aortic insufficiency, the characteristic murmur may disappear entirely with severe congestive failure and reappear with myocardial improvement. Very rarely a murmur of aortic insufficiency may result from anemia, probably due to dilatation of the ring; in such a case, however, the anemia is usually severe and the differentiation is not difficult.

Combined Mitral and Aortic Valvular Disease

Combined deformity of mitral and aortic valves is much less frequent than mitral damage alone, but it may present a very serious problem and it is imperative that the surgeon know preoperatively if both valves are involved. Aortic insufficiency is usually recognized easily, but if severe aortic stenosis is not corrected when the mitral stenosis is relieved, the inability of the heart to adjust to the changed dynamics may be fatal.

Pulmonary Valvular Disease

Pulmonary valve disease is almost always congenital. If stenosis is present there is a rough systolic murmur. Diminution or absence of the second sound depends upon whether the predominant stenosis is valvular or infundibular and on other anomalies. Insufficiency of slight degree associated with the stenosis usually is not of dynamic significance. With a dilated ring and relative insufficiency, usually the result of very severe and long-standing mitral valve damage, an early diastolic murmur may be heard. It is usually short and rough instead of blowing in character. Sometimes the murmur is heard a very short interval after the second sound, which is usually accentuated. The differentiation of pulmonic from aortic valve involvement usually is not difficult, particularly when the shape of the cardiac silhouette, the electrocardiogram and pressures are studied.

Tricuspid Valvular Disease

Auscultation is of relatively little help in the diagnosis of tricuspid lesions. Stenosis is almost always associated with severe mitral deformity of rheumatic origin; with it a mid-diastolic snap is said to occur in the fourth right interspace near the sternal border. Unfortunately it is not always present, and for the most part the diagnosis depends upon other means of

examination, i.e., usually a very large right atrium and venous pressure curves. The patient with severe mitral stenosis who has had an adequate commissurotomy and who does not show the expected postoperative improvement should be suspected of having a tricuspid lesion. Insufficiency of this valve certainly cannot be diagnosed by auscultatory means. A systolic murmur at the lower left sternal border of different character from an associated mitral murmur is not dependable. Other signs, i.e., a pulsating liver (not transmitted pulsation from an abdominal aorta), intractable ascites and at times pulsation of a small distended vein in the upper anterior chest, carry much more weight.

In view of the increasing tendency to visualize heart sounds, a word of caution is in order. The usual phonocardiogram or oscilloscopic curve portrays the complex grouping of tone, intensity and time, which make up sounds and murmurs, but the equipment used to produce, record and reproduce heart sounds is of critical importance, particularly the pickup (microphone) and amplifier. If they are not capable of responding to the frequencies that make up heart sounds, the result is incorrect. Furthermore, comparison of records made at different times may be erroneous because of changed characteristics of the pickup or amplifier. No microphone is available today that responds to these vibration frequencies in the order of their magnitude; present-day visual records, time, i.e., phonocardiograms, oscilloscopic trace and cardiospectrograms, may well show an untrue picture of the relative amplitude of the different vibration patterns that are transmitted through the chest wall. Because this pattern includes some of the inaudible part of the sound spectrum, at times one does not hear what is seen; with no amount of practice can anyone hear below a certain frequency range. The visual and the auditory methods have specific merits that cannot be translated from one to the other. It may be misleading to assume that in a particular instance graphic registration is the last word. This difference is well illustrated by the position in the cardiac cycle of the murmur of mitral stenosis. Mitral stenotic murmurs invariably are heard in mid-diastole or late diastole, yet one reads of some murmurs of mitral stenosis being holodiastolic. According to auscultation this is incorrect, even though at times certain frequencies of this murmur may be seen on an oscilloscope trace during the entire period of diastole. Part of this trace shows vibrations in the inaudible part of the spectrum. As yet, the visible electronic method is often particularly deficient in clearly distinguishing whether the character of a murmur is rough, blowing or musical, in differentiating patterns of third heart sounds, such as the lilt of a gallop rhythm compared with a normal heart and loud third sound at a rate over 100 per minute and the difference between an opening snap and a short mid-diastolic murmur.

While the future will certainly provide electronic means for the better appraisal of the complex vibration patterns that make up auscultatory phenomena, our major teaching effort at this time must be directed toward the better use of knowledge that is already at hand. Fortunately the trend is in that direction.

SPECIAL COMMITTEE REPORT

Standards for Centers Caring for Patients with Congenital Cardiac Defects

Report of the Subcommittee on Education and Standards in the Field of Congenital Heart Disease

THE purpose of this report is to provide standards for services and necessary equipment for centers responsible for the diagnosis and surgical care of patients with congenital defects of the heart and blood vessels.* Skill in this field is dependent on training and on continuous extensive experience which in turn is related to the caseload of an institution. Before establishing such a center, careful consideration should be given to the real need in the city or area for this highly specialized type of diagnostic workup and surgical correction. Many skills and facilities needed are not ordinarily available outside a medical center.

Accurate diagnosis of the congenital cardiac malformation is a prerequisite to cardiac surgery. To have a diagnostic center for this purpose is, therefore, of prime importance for any hospital in which cardiac surgery is performed.

This type of work requires highly developed teamwork on the part of the pediatric or medical diagnostician, surgeon, anesthesiologist, roentgenologist and members of allied services. It is not advisable to have a sharp division between diagnostic and surgical responsibilities. The center in which cardiac surgery is done must be ultimately responsible for both definitive diagnosis and surgical care. The essential requirements for a diagnostic center follow below.

This report of the Subcommittee on Education and Standards in the Field of Congenital Heart Disease appointed by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association reflects that committee's findings in the matter under study.

* This report serves to augment the *Recommended Standards for Cardiovascular Clinics*.[1]

I. Staff

A. *Physicians.* The following specialists should be on the team:

1. A *pediatric cardiologist* or a *cardiologist* who is thoroughly familiar with the diagnostic features and care of patients with congenital cardiac malformations is essential. The importance of a pediatrician on the team is evident when it is realized that more than one half of such patients are in the pediatric age group.

2. A qualified *radiologist* who has had additional training in the cardiovascular field.

3. A qualified *surgeon* with training in cardiovascular surgery who should be directly responsible for the surgical care of the patients.

4. A *physician-anesthesiologist* with experience in cardiovascular surgery and open-chest anesthesia is mandatory.

5. The *team* which is capable of performing *cardiac catheterization and angiocardiography*, conforming to the standards established by the two reports of the Committee on Cardiac Catheterization and Angiocardiography of the American Heart Association.[2, 3]

A well-trained *pathologist* familiar with the problems of the physiologist, the cardiologist and the surgeon can assist the team in many ways. Extensive

pathologic study should be made, if possible, on all patients who do not survive and the pathologic findings should be regularly reviewed by the whole group.

The Registry of Cardiovascular Pathology sponsored by the American Heart Association in cooperation with the Armed Forces Institute of Pathology, Washington 25, D. C., can supply pathologists and other members of the staff with material that may assist in the education of the physician in malformations of the heart, particularly those of surgical significance. The Institute will, upon request, also work up material if local facilities do not permit a thorough study.

B. *Nurses.* Outpatient and inpatient departments should have registered professional nurses familiar with the care of patients undergoing diagnostic study and cardiovascular surgery. It is preferable that the *clinic* nurse has public health experience and is capable of assisting families to secure nursing supervision at home. The *hospital* nursing care must be under the close supervision of nurses familiar with needs of such cardiac patients. Expert and individual nursing care must be continued during the postoperative period for as long as it is medically advisable.

C. *Medical Social Worker.* A qualified medical social worker should be a full-time member of the staff. Medical social service should be available during *all* stages of care irrespective of economic status because of the anxiety, fear and worry in the family when cardiac surgery is considered. The case worker should be willing to aid in *all* social problems and must be experienced in the socioeconomic conditions usually found in such families, often young and inexperienced families. Both the medical social worker and the nurse (or public health nurse) should work together with the health and social agencies in the patient's community to establish optimum care for the patient.

II. Diagnostic Facilities

A. *General:* The following facilities, usually provided in a clinic, should be available:

(1) Fluoroscopy and x-ray,

(2) electrocardiography, and

(3) a laboratory for routine analysis of blood and urine.

B. *Special:* The following special facilities are mandatory:

(1) Bacteriology laboratory,

(2) blood chemistry laboratory,

(3) medication and oxygen at close hand for emergencies and

(4) laboratory and equipment for cardiac catheterization, angiocardiography and aortography, conforming to the standards set by the Committee on Cardiac Catheterization and Angiocardiography;[2, 3] this laboratory must be equipped for determination of oxygen saturation of arterial blood. It is desirable also to have a cardiopulmonary laboratory.

III. Diagnostic Services to the Patient

A. *Outpatient Department.* In many instances, the diagnosis of the congenital cardiac defect can be established on an outpatient visit by means of a complete medical history, physical examination, fluoroscopic examination, x-ray, electrocardiogram and laboratory studies for blood and urine. The cardiologist should be able to fluoroscope all patients as a part of his examination.

B. *Inpatient Department.* It is well to recognize that some patients with congenital cardiac defects suffer from anoxemia, polycythemia or cardiac decompensation and require hospitalization and careful medical management during the period of diagnostic evaluation. Facilities for special diagnostic studies should be available to aid in a definitive diagnosis of all patients when necessary. Those patients in need of such studies as cardiac catheterization, angiocardiography or aortography should be hospitalized likewise for these procedures. It is preferable to have all diagnostic patients admitted to the medical or pediatric service of the medical center.

C. *Teamwork.* All members of the staff or team should work together in the evaluation of the patient's condition and in making decisions, but one staff physician should be solely responsible for the individual patient. The diagnostic team should have experience in the interpretation of cardiac catheterization findings in conjunction with the complete

clinical picture; never should cardiac catheterization or angiocardiographic findings be considered alone. It is desirable to hold regularly scheduled *cardiovascular conferences* to discuss not only individual cases but changes in general concepts of cardiovascular surgery.

IV. Basic Requirements in the Surgical Care of Patients

A. A qualified *surgeon* with training and experience in cardiovascular surgery, including the use of arterial grafts, should be directly responsible for the surgical care of patients. He should have sufficient experience to meet with confidence the innumerable unusual situations that may arise.

B. There should be a full-time *resident* surgical and medical *staff* in the hospital, capable of dealing with all problems that arise following surgery.

C. Nursing supervision and care by *nurses* familiar with the needs of patients undergoing cardiovascular surgery are essential. It is highly desirable to have specialized nursing care provided in a recovery unit on a 24 hour basis. These nurses should be trained in the aftercare of patients undergoing cardiovascular surgery. Special nursing care should be given as long as it is medically advisable.

D. A *physician-anesthesiologist* who has had experience with patients undergoing cardiovascular surgery and open-chest anesthesia is mandatory.

E. *Special equipment* such as various types of needed oxygen apparatus, blood bank facilities, cardiac resuscitation or tracheotomy sets should be available through each 24 hours.

F. A source of *arterial grafts*[4] should be available to a surgical staff member who is experienced in using them.

G. The operating room should be thoroughly equipped with all the advisable *surgical instruments* especially devised for intrathoracic and cardiovascular work as well as those commonly required for general surgery.

H. A *recovery unit* or its equivalent is important in providing special care and attention during the early hours after operation and advisedly should be open on a 24 hour basis.

The highly specialized staff and the facilities mentioned above are considered basic and are often not available outside a medical center that constantly cares for such patients.

V. Aftercare

A. *Staff Care and Evaluation of Patient.* It is essential that the medical staff at all times work closely with the surgeon and evaluate the results of surgery and the patient's cardiac reserve prior to discharge. Usually it is the responsibility of the cardiologist or pediatrician to assess the patient's cardiac reserve and to make recommendations concerning resumption of his activities.

The medical social worker and public health nurse should be available to assist with plans upon discharge of the patient from the hospital. They should follow through with referrals to the patient's local community, when indicated. The aim of both nurse and medical social worker should be to work together and to aid in follow-up planning, in order to achieve the best possible adjustment and rehabilitation of patient and family.

B. *Contact with Referring Physician.* The referring physician should be kept informed at all stages of the diagnostic study and care. He should be advised concerning:

(1) The indications and recommendation for surgery,

(2) the results of operation, including the occurrence of any postoperative complications and

(3) the condition of the patient at the time of discharge from the hospital.

Recommendations for future medical management and follow-up after discharge are necessary for all cardiac patients.

C. *Follow-up:* It is advisable that the center request follow-up visits in order to obtain

accurate evaluation of the operative results over a long period of time and, in turn, to send this information to the referring physician to assist him in his future management of the patient. It is sincerely hoped that all diagnostic and surgical centers will carefully evaluate their long-term operative results.

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SPECIAL COMMITTEE REPORT

Jones Criteria (Modified) for Guidance in the Diagnosis of Rheumatic Fever

Report of the Committee on Standards and Criteria for Programs of Care

MAJOR CRITERIA

I. Carditis

II. Polyarthritis

III. Chorea

IV. Subcutaneous Nodules

V. Erythema Marginatum

MINOR CRITERIA

I. Fever

II. Arthralgia

III. Prolonged P-R Interval in the Electrocardiogram

IV. Increased Erythrocyte Sedimentation Rate, Presence of C-reactive Protein or Leukocytosis

V. Evidence of Preceding Beta-hemolytic Streptococcal Infection

VI. Previous History of Rheumatic Fever or the Presence of Inactive Rheumatic Heart Disease

IN 1944, the late Dr. T. Duckett Jones published criteria for the diagnosis of rheumatic fever which have been generally accepted in the United States and in many parts of the world. Subsequently Dr. Jones guided the revision of his criteria for use in the United Kingdom-United States Cooperative study on "The Relative Effectiveness of ACTH, Cortisone and Aspirin in the Treatment of Rheumatic Fever" and, just prior to his death, he participated in a conference on the revision of his original suggestions for use by the practicing physician. These modified Jones criteria are based in great measure upon his suggestions.

Rheumatic fever is related to previous infection with group A β-hemolytic streptococci, but the mechanism of the disease is unknown. Its boundaries are indefinite, and its differentiation from other diseases is sometimes impossible. There is no specific laboratory diagnostic test. The diagnosis must therefore be arbitrary and empirical. Criteria herein set forth are aimed at identifying those individuals who have had or are having an attack of rheumatic fever. They make no attempt to measure rheumatic activity at any given time or to diagnose inactive rheumatic heart disease. Thus, following the designation of an illness as rheumatic

This is a report of the Committee on Standards and Criteria for Programs of Care of the Council of Rheumatic Fever and Congenital Heart Disease of the American Heart Association and has been approved by the Executive Committee of that Council.

fever, the existence of continued activity or the presence of inactive rheumatic heart disease may be indicated by criteria different from those outlined below.

Criteria are necessary in order to minimize both overdiagnosis and underdiagnosis. The tendency to label as rheumatic fever a chronic febrile illness for which no obvious cause can be found is to be deplored. The tragedy which may lie in the wake of the false diagnosis of rheumatic fever may be even greater than the possible harm of missed recognition in questionable cases. The institution of effective prophylactic regimens requiring prolonged administration of sulfadiazine or antibiotic agents places a grave responsibility on the physician in the diagnosis of this illness.

In this statement, the diagnostic features of the disease are divided, as originally proposed by Jones, into major and minor categories, dependent upon their relative occurrence in rheumatic fever and in other disease syndromes from which this disease must be differentiated. Thus, chorea is included among the major criteria while fever, a symptom common to many diseases, is placed in a minor category. *These major and minor categories have no significance beyond their diagnostic import either as to prognosis, amount of "rheumatic activity" or severity of acute illness.* Indeed, a severe manifestation of rheumatic fever, such as rheumatic pneumonia, is not included because it is difficult to differentiate from congestive cardiac failure and because it almost always occurs in patients whose rheumatic fever is so obvious as to offer no difficulty in diagnosis.

The presence of two major criteria or one major and two minor criteria indicates a high probability of the presence of rheumatic fever (with one notable exception, see Other Manifestations). In addition to the major and minor criteria to be used in the recommended formula, other manifestations have been listed which may be used to support the diagnosis. These criteria are not meant to substitute for the wisdom and judgment of the clinician. They are designed only to guide him toward a diagnosis of the disease with the suggestion that he follow carefully all questionable cases and restrict the diagnosis of rheumatic fever to illnesses which meet acceptable criteria.

Major Diagnostic Criteria

I. *Carditis*

As evidenced by any one of the following:

A. The presence of a significant apical systolic murmur,* apical mid-diastolic murmur† or basal diastolic murmur‡ in an individual without a history of previous rheumatic fever or in whom there is good reason to believe there was no pre-existing rheumatic heart disease; or a change in the character of any of these murmurs under observation in an individual with previous history of rheumatic fever or rheumatic heart disease.

B. Obviously increasing cardiac enlargement determined by x-ray study.

C. Pericarditis manifested by a friction rub,

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* *A significant apical systolic murmur* is long, filling most of systole; is heard best at the apex; is as well transmitted toward the axilla as over the precordium; and does not change with position or respiration. It must be differentiated from an innocent (functional) murmur which is frequently found in normal people. This innocent murmur is systolic, occasionally harsh, is heard best along the left sternal border and usually changes with position and respiration. Borderline systolic murmurs, intermediate in location and nature, occur and should be carefully watched. Questionable murmurs which are intermittently present or which, after a period of observation cannot be clearly classified as significant, are rarely of any import.

† *A significant organic apical systolic murmur* is frequently accompanied by a low-pitched, short *mid-diastolic murmur* which is sharply localized to the chest wall over the apex of the heart and often heard best with a patient in the left lateral position with the breath held in expiration. This murmur, rarely present in the absence of an apical systolic murmur, confirms the significant nature of the latter. It must be differentiated from the long, low-pitched, crescendo apical presystolic murmur followed by an accentuated mitral first sound which is indicative of mitral stenosis but not of acute carditis.

‡ The development of a *basal diastolic murmur* of aortic insufficiency is also indicative of carditis. It is an early, short, diminuendo murmur usually heard only or heard best along the left sternal border in deep expiration. It has great diagnostic value, even though it may be difficult to hear and present only intermittently.

pericardial effusion or definite electrocardiographic evidence.

D. Congestive heart failure present (in a child or young adult under 25) in the absence of other causes.

II. *Polyarthritis*

Polyarthritis tends to be migratory and is manifested by pain *and* limitation of active motion, or by tenderness, heat, redness or swelling of two or more joints. Arthralgia alone without objective evidence of joint involvement is not a major manifestation.

III. *Chorea*

This must be differentiated from habit spasm, athetosis and cerebellar ataxia. Movements must be characteristic, involuntary and of moderate severity if chorea is to be used as a major manifestation.

IV. *Subcutaneous Nodules*

Subcutaneous nodules are shot-like, hard bodies seen or felt over the extensor surface of certain joints, particularly elbows, knees and wrists, in the occipital region, or over the spinous processes of the thoracic and lumbar vertebrae.

V. *Erythema Marginatum*

This recurrent, pink, characteristic rash of rheumatic fever, in which the color gradually fades away from its sharp scalloped edge, is found mainly over the trunk, sometimes on the extremities, but not on the face. It is transient, is brought out by heat and migrates from place to place.

Minor Diagnostic Criteria

I. *Fever*

A significant rise in temperature is a common symptom, but, because it occurs in so many illnesses, it has little differential diagnostic value. In order to be included, the elevation in temperature must clearly exceed the normal diurnal fluctuation in which there is great individual variation.

I. *Arthralgia*

Pain clearly located without objective findings is only a minor criterion for diagnosis. The pain must be in the joint, not in the muscles or other periarticular tissues, and must be distinguished from the nocturnal pain in the extremities occurring in normal children. Arthralgia must not be used as a minor criterion when polyarthritis is included as a major criterion.

III. *Prolonged P-R Interval in the Electrocardiogram*

Prolongation of the P-R interval may be nonspecific; it is considered a minor criterion and is not diagnostic of carditis. It cannot be used if carditis is already included as a major manifestation.

IV. *Increased Erythrocyte Sedimentation Rate, Leukocytosis, or Presence of C-reactive Protein*

Elevation in one or more of these nonspecific tests may be considered as a single minor criterion. Particularly to be deplored is the tendency to use any of these tests as a major criterion or as diagnostic of rheumatic fever. There are many other nonspecific tests, but these three are most commonly used.

V. *Evidence of Preceding Beta-Hemolytic Streptococcal Infection*

This must be documented by (1) a history of scarlet fever or by a typical clinical picture of other streptococcal infection, preceding the onset of rheumatic fever by one week to one month, the nature of the infection being confirmed by a history of immediate contact with other individuals having typical streptococcal infection or by positive culture of the nose or throat in which β-hemolytic streptococcus predominates or (2) an elevated or rising antistreptolysin-O titer.

VI. *Previous History of Rheumatic Fever or the Presence of Inactive Rheumatic Heart Disease*

The existence of either of these may be used as a minor criterion to aid in deciding the rheumatic nature of the illness in question. For this use, the previous history must be documented by the same objective criteria as are set forth in this statement or by the presence of inactive rheumatic heart disease.

Other Manifestations

These include systemic manifestations, such as loss of weight, easy fatigability, elevated sleeping pulse rate (tachycardia out of proportion to fever), malaise, sweating, pallor or anemia and local manifestations such as epistaxis, erythema nodosum, precordial pain, abdominal pain, headache and vomiting. These, as well as a family history of rheumatic fever, provide additional evidence of the presence of rheumatic fever, but are not to be included as diagnostic criteria.

Combinations of these diagnostic criteria that occur in the presence of other illnesses must be ruled out before a definitive diagnosis is made. One combination in particular, polyarthritis, fever and elevated sedimentation rate, is the weakest of all combinations of major and minor criteria. Diseases to be ruled out include rheumatoid arthritis, gonococcal arthritis, lupus erythematosus disseminatus, subacute bacterial endocarditis, nonspecific pericarditis with effusion, leukemia, sickle cell anemia, serum sickness (including manifestations of penicillin sensitivity), tuberculosis, poliomyelitis, undulant fever and septicemias, particularly meningococcemia.

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BACTERIAL ENDOCARDITIS

Feder, I. S.: Treatment of Subacute Bacterial Endocarditis with Negative Blood Cultures. Am. J. Med. **18:** 602 (April), 1955.

The treatment of subacute bacterial endocarditis is discussed and the need for early, intensive and prolonged treatment is stressed. The management of cases with negative blood cultures is outlined. It has been the practice of the author, in all suspected cases of subacute bacterial endocarditis, to draw blood for culture at least twice on the day of admission and daily thereafter for three days before definitive therapy is started. As soon as a positive culture is obtained, the sensitivity of the organism against the various antibiotics is tested even before it is identified. If the organism is entirely resistant to penicillin, the antibiotic to which the organism is most sensitive is administered in adequate dosage by the best route available for at least five weeks. If it is penicillin-sensitive, 10 million units of penicillin, dissolved in 1 liter of 5 per cent glucose in water in which 10 mg. of heparin are added to prevent thrombosis at the site of venipuncture, are given intravenously over 24 hours. Benemid has been given simultaneously at times. Occasionally, streptomycin or dihydrostreptomycin in divided doses of 2 to 3 Gm. daily have been added intramuscularly. In patients suspected of having subacute bacterial endocarditis with negative blood cultures, the author initiates therapy with 10 million U of penicillin daily intravenously, with 2 to 3 Gm. of streptomycin or dihydrostreptomycin in divided doses daily intramuscularly. If these are therapeutically effective, the temperature should become normal in 48 to 72 hours. Should this not occur, the dose of penicillin may be doubled and Benemid added. If within another 24 hours, the temperature has not become normal or appreciably lower, both drugs are discontinued, and one or a combination of the other antibiotics is started. If penicillin and streptomycin are partially but not completely effective, they are continued, and one or another antibiotic, and at times a triple sulfonamide, is added. When the effective drug or combination of drugs is found, treatment should be continued in the maximum dosage for at least five weeks, unless severe reactions occur to contraindicate their use.

HARRIS

Priest, W. S. and Smith, J. M.: The Effect of Healed Subacute Bacterial Endocarditis on Cardiac Dynamics. Arch. Int. Med. **95:** 656 (May), 1955.

On the basis of this study of 16 patients, alive approximately 10 years after recovery from bacterial endocarditis, the following points can be brought out: Bacterial endocarditis adequately treated does not appear to be as damaging to the heart as was previously believed. The ultimate fate of the large majority of patients cured of bacterial endocarditis is determined not by the residuals of the bacterial process, but by the severity or nature of the pre-existing cardiac damage or anomaly, and the subsequent presence or absence of rheumatic activity, coronary artery disease and hypertension. Severity of the myocarditis, incident to the active phase of bacterial endocarditis, plays a greater part in determining future cardiac impairment than does residual valve damage. The duration of activity of the infectious process prior to therapy does not seem to influence the future prognosis. Careful roentgen study in four projections, plus careful clinical evaluation, gives practically as much information concerning the severity of pre-existing and subsequent cardiac damage as does cardiac catheterization. Cardiac catheterization is necessary when there is a question as to the exact anatomic diagnosis, or when the severity of subjective symptoms is out of proportion to the physical, roentgen and electrocardiographic findings.

BERNSTEIN

BLOOD COAGULATION

McKay, D. G., Hardaway, R. M., III, Wahle, G. H., Jr., Edelstein, R., and Tartock, D. E.: Alterations in Blood Coagulation Mechanism after Incompatible Blood Transfusion. Clinical and Experimental Observations. Am. J. Surg. **89:** 583 (Mar.), 1955.

Experiments were performed on dogs for the purpose of studying the effects of incompatible blood transfusion on the blood coagulation mechanism. One group of animals was given 100 mg. of cortisone a day for 3 days preceding the transfusion. Another had either no preparation or was dehydrated for 3 days prior to transfusion.

Clinical hemorrhage occurred in all but two of the experiments. The most constant finding was gross blood in the stools. The hemorrhagic diathesis was associated with thrombocytopenia, prolongation of the coagulation and prothrombin times and a decrease in the number of circulating white blood cells. There was also the appearance of fibrinolytic activity, and of a circulating anticoagulant with some of the properties of heparin.

Pretreatment with cortisone caused an elevation of the white blood count and a greater and more rapid decrease in the fibrinogen concentration in the first hour following incompatible blood transfusion. Cortisone also seemed to be responsible for an increase in the tendency to coagulation in this reaction.

On the basis of their findings, the authors suggested that in the case of incompatible blood transfusion, the medical management should involve a complete, immediate estimate of all the major blood clotting factors with a subsequent replacement of fibrinogen, or the use of an antiheparin agent wherever indicated.

ABRAMSON

CONGENITAL ANOMALIES

Eldridge, F. L. and Hultgren, H. N.: Pulmonary Stenosis with Increased Pulmonary Blood Flow. Am. Heart J. **49:** 838 (June), 1955.

Eight cases of pulmonic stenosis with increased pulmonary blood flow are described. Four had an interventricular septal defect, three an atrial septal defect and one, an aortic-pulmonary artery communication. The essential clinical features consist of a combination of the signs of an atrial or an interventricular septal defect associated with those of a pulmonic stenosis. Increased pulmonary vascular markings, which are seen by x-ray, caused the pulmonic stenosis to be overlooked in 7 of the 8 cases. In five cases, the pulmonic second sound was accentuated. Surgery should be directed toward closure of the septal defect where this is possible, since the degree of pulmonic stenosis is usually mild and further enlargement of the valve orifice may only increase the magnitude of the left-to-right shunt.

RINZLER

Mustard, W. T., Rowe, R. D., Keith, J. D. and Sirek, A.: Coarctation of the Aorta with Special Reference to the First Year of Life. Ann. Surg **141:** 429 (April), 1955.

The authors analyzed a group of patients less than one year of age with postductal coarctation and another group suffering from the infantile or preductal type of coarctation.

The diagnosis of postductal coarctation is suspected in an infant, if a heart murmur or dyspnea or both are present, associated with impalpable femoral arterial pulsations and higher blood pressure readings in the arm than in the leg. An aortogram is of considerable value in differentiating postductal from preductal types under one year since it will demonstrate the extent of narrowing of the aorta, and may show a ductus arteriosus.

In the preductal group, there may be signs of dyspnea and heart failure, as in the case of the postductal type, and also a heart murmur. In some cases, however, pulsations may be present in the femoral artery.

Because of the high mortality (89 per cent) in the preductal type of coarctation, the authors advise almost immediate surgical intervention. In the case of the postductal type, approximately 60 per cent of babies, who present signs or symptoms in the first year of life, die during that period. Therefore, potentially fatal cases should likewise be operated upon. Surgical excision should be performed.

ABRAMSON

Mannix, E. P., Jr., and Haight, C.: Anomalous Pulmonary Arteries and Cystic Disease of the Lung. Medicine **34:** 193 (May), 1955.

The authors report 15 cases of anomalous pulmonary arteries associated with cystic disease of the lung (including cystic bronchiectasis). The embryology and anatomy of anomalous pulmonary vessels are reviewed and the clinical literature is surveyed. The lung parenchyma supplied by the anomalous vessel may be normal, may be congenitally malformed or the site of an acquired pathologic process. In all but one of the authors' cases, a congenital pulmonary cyst or cystic bronchiectasis was the primary pulmonary lesion. The anomalous artery usually arises from the aorta or an aortic branch, the most common origin being the lower thoracic aorta.

The presence of an anomalous pulmonary artery should be suspected in any patient with cystic disease, especially of the lower lobes, with onset of symptoms early in life. This is because the only effective treatment is resection of the involved portion of lung. If the incidence of anomalous

rteries associated with cystic disease is not appreciated, serious and even fatal hemorrhage may ccur during surgery.

ENSELBERG

Moss, A. J.: Coarctation of the Aorta in Siblings. J. Pediat. **46:** 707 (June), 1955.

Coarctation of the aorta in two siblings is described. One child, a boy, was eight years of age at the time he was examined and successfully operated. A female sibling, born after the first child was operated upon, was examined and operated upon successfully at the age of three years. The incidence of familial congenital cardiac abnormalities is discussed.

HARVEY

Sepulveda, G., Lukas, D. S. and Steinberg, I.: Anomalous Drainage of Pulmonary Veins. Am. J. Med. **18:** 883 (June), 1955.

Three cases of partial and three of total anomalous pulmonary venous drainage into the right atrium or its tributaries are reported. The main clinical, physiologic and angiocardiographic features are discussed. Among the group with partial anomalous pulmonary venous drainage, one case was uncomplicated and asymptomatic. Two with symptoms had associated defects. All patients with total anomalous drainage of the pulmonary veins had symptoms, and two were cyanotic. Similarity of blood oxygen contents in the right ventricle, pulmonary and systemic arteries is a diagnostic feature of this anomaly. A filling defect produced by turbulence of the contrast material at the site of insertion of the anomalous vein was observed in the angiocardiogram of five cases. This previously unrecognized sign was of great value in establishing the diagnosis and permitting differentiation from an uncomplicated interatrial septal defect.

Roentgenography is the most important simple examination which may reveal the diagnosis of transposition of the pulmonary veins. An anomalous right pulmonary vein draining into the inferior vena cava usually appears in the roentgenogram as a broad branching channel which curves in crescentic fashion near the right cardiac border, and descends toward the right cardiohepatic region. Usually the right atrial silhouette is prominent because of the increased blood flow. Pulmonary veins inserting into the left innominate vein also have a characteristic x-ray appearance. Whether the anomalous drainage is partial or complete, there is a wide channel (a persistent left superior vena cava) at the left hilum and superior mediastinum. As a result of the large blood flow it transmits, the right superior vena cava dilates and forms a bulge in the right superior mediastinal silhouette.

HARRIS

Towers, D., Burchell, H. B. and Wood, E. H. Difficulty in the Precise Localization by Cardiac Catheterization of Left-to-Right Shunts Near the Pulmonary Valve. Proc. Staff Meet., Mayo Clin. **30:** 261 (June), 1955.

When, in the same patient, the oxygen content of the blood in the pulmonary artery is higher than that in the right ventricle and the oxygen content of the blood in the right ventricle is itself higher than that in the right atrium, left-to-right shunts may be present above, below or both above and below the pulmonary valve. Unless the cardiac catheter can be manipulated through the defect (or defects) responsible for the shunts, presently available diagnostic technics may fail to demonstrate the precise location of the underlying defect (or defects). In the presence of a demonstrated aortopulmonary shunt, presently available diagnostic technics may fail to exclude the possibility of an associated interventricular shunt.

SIMON

Eldridge, F. L. and Hultgren, H. N.: The Physiologic Closure of the Ductus Arteriosus in the Newborn Infant. J. Clin. Invest. **34:** 987 (July), 1955.

The oxygen content of blood obtained from the upper and lower extremities was studied in 60 infants of various ages. From the differences in hand-foot oxygen saturation, it appears that in the new-born infant the ductus arteriosus is patent and is the site of a veno-arterial shunt of some magnitude for at least three hours after birth in about 30 per cent of infants. Calculations indicate that this shunt may contribute as much as 72 per cent of the total blood flow in the descending aorta.

The influence of crying upon pressure relationships is unknown but it is quite possible that an increase in intrathoracic pressure on crying may cause a veno-arterial shunt to occur through the ductus where none was apparent at rest. It is suggested that a fall in pulmonary artery pressure to a level below the aortic pressure caused the disappearance of the hand-foot oxygen saturation difference rather than actual closure of the ductus arteriosus.

The data demonstrate that physiologic closure of the ductus may take place later than had previously been supposed. It is interesting that only one of 43 newborn infants had a murmur in spite of the physiologic patency of the ductus arteriosus.

WAIFE

Bashour, F. and Winchell, P.: Preponderant Left-to-Right Flow Through a Ventricular Septal Defect in the Presence of Pulmonary Stenosis. Ann. Int. Med. **42:** 1227 (June), 1955.

At this time it would seem unwise to recommend a simple pulmonary valvulotomy for the patient with pulmonary stenosis and a left-to-right shunt through a ventricular septal defect. In these cases, the ideal procedure would be to combine pulmonary valvulotomy with closure of the septal defect. In

three cases of Fallot's tetralogy studied by cardiac catheterization, it was found that the preponderant shunt at rest was from left to right instead of from right to left. The most important factor in determining the pressure gradient, and hence the direction of flow across the defect, seems to be the severity of the pulmonary stenosis. The shunt may reverse with exercise, since an increased cardiac output in the presence of a fixed right ventricular outflow tract resistance may elevate the right ventricular pressure to a level in excess of that in the left ventricle. Cyclic variations in the pressure gradient across the septal defect may account for slight arterial unsaturation at rest, although the major flow is from left to right.

WENDKOS

Blount, S. G., Mueller, H. and McCord, M. C.: Ventricular Septal Defect. Clinical and Hemodynamic Patterns. Am. J. Med. **18:** 871 (June), 1955.

The clinical and hemodynamic data of 24 patients with ventricular septal defects indicate that the size of the ventricular defect constitutes the major anatomic variable in this anomaly and determines the resultant clinical and hemodynamic pattern. No surgical measures are indicated in patients with small ventricular septal defects in whom there is no significant pulmonary hypertension, and where left to right shunts are of small magnitude. Patients with large defects presenting severe pulmonary hypertension, marked increase in pulmonary vascular resistance, and left to right or right to left shunts of small volume probably have passed the stage where closure of the ventricular defect would produce significant beneficial results. The ideal candidates for closure of ventricular septal defects are, therefore, patients presenting mild to moderate increase in pulmonary hypertension, slight to moderate increase in pulmonary vascular resistance and left to right blood flow of high magnitude.

The electrocardiogram was found to be a diagnostic aid and of significance in estimating the magnitude of the physiologic abnormalities. A normal electrocardiogram in a patient with auscultatory evidence suggesting a ventricular septal defect, indicated an absence of significant pulmonary hypertension and an absence of significant increase in pulmonary blood flow. The presence of high amplitude equiphasic QRS complexes in the midprecordial positions was a characteristic feature of the electrocardiogram in patients with ventricular septal defects. This finding was interpreted as suggesting hypertrophy of both ventricles. A definite left ventricular hypertrophy pattern was associated with large left to right shunts in the absence of severe, pulmonary hypertension. The dominance of a right ventricular hypertrophy pattern in the precordial leads in patients with ventricular septal defects was associated with marked pulmonary hypertension and left to right shunts of small magnitude. This finding was considered to suggest a late stage in the natural course of the disease.

HARRIS

CORONARY ARTERY DISEASE

Marchand, W. E.: Occurrence of Painless Myocardial Infarction in Psychotic Patients. New England J. Med. **253:** 51 (July 14), 1955.

This study was undertaken to evaluate the role of a psychosis in painless myocardial infarction. A group of 51 patients with acute myocardial infarction occurring in a mental institution were analyzed. Of these, 26 were diagnosed schizophrenic and 1 had general paralysis of the insane. Rupture of the left ventricle occurred in four cases, and rupture of the interventricular septum developed in one case. The author reports an incidence of rupture of the heart as the cause of death in 21.7 per cent of a small group of cases in which sudden death occurred in this institution, as contrasted with an incidence of 2.1 per cent in sudden death occurring in the general population. This is felt to support the contention that myocardial infarction does occur in these institutionalized patients without complaints of pain or other signs or symptoms which might bring them to the attention of the hospital personnel.

There were 52 acute myocardial infarctions in the 51 patients studied. The presenting signs or symptoms included weak spell or collapse, chest pain, dyspnea, cyanosis or sudden death. Four patients were discovered because of an abrupt change in their psychotic behavior. Two patients were diagnosed by sheer chance, one as electrocardiograms were being done to check serum potassium levels, and the other when an electrocardiogram was being taken as a control observation, prior to the observation of the effect of sodium amobarbital upon mutism. Painless myocardial infarction occurred in 82.5 per cent of the cases, a figure which dropped to 67.5 per cent when the symptoms during the first 24 hours were analyzed. It is the belief of the writer that the meaning of pain is lost to the majority of patients with organic or functional psychoses and for this reason they are nonresponsive to painful processes.

ROSENBAUM

Wasserman, F., Bellet, S. and Saichek, R. P.: Postoperative Myocardial Infarction. Report of Twenty-Five Cases. New England J. Med. **252:** 967 (June 9), 1955.

This report is concerned with 25 cases of postoperative myocardial infarction observed over a period of six years at the Graduate Hospital, Philadelphia. These 25 cases occurred in a series of approximately 37,000 operations, 21 followed major operations and 4 followed minor procedures. Nineteen patients showed clinical evidence of heart disease prior to surgery and of the others, one had diabetes mellitus and one had pulmonary fibrosis.

Twenty-one received general anesthesia; in seven, a muscle relaxant was used. Two received spinal anesthesia and two were operated upon under local anesthesia. A drop in blood pressure of 40 mm. systolic and 20 mm. Hg diastolic, or greater, occurred in 12 patients. The myocardial infarction occurred on the day of or within seven days of the operation in 92 per cent of the patients, and during the second postoperative week in the remainder. The typical clinical picture of acute myocardial infarction was observed in only eight patients. The usual clinical manifestations developed in only one-half of the cases; typical pain was present in one-third and hypotension was present in two-thirds of the patients. Five patients died, three of them directly due to the myocardial infarction, one from uremia and the other from septicemia with severe electrolyte imbalance. The authors believe that in the group of patients whose electrocardiographic changes consisted of inverted T waves, these abnormalities were due to ischemic and anoxic changes, resulting from hypotension, leading to subendocardial infarction often without occlusion of a major coronary artery. Among the factors predisposing to postoperative myocardial infarction, the authors mention cardiac enlargement and hypertension, coronary artery disease, congestive heart failure, valvular disease, particularly aortic stenosis, anemia and polycythemia, infections, electrolyte disturbances, anesthetic agents which cause anoxia, hypercapnia and hypotension, hemorrhage and visceral manipulations during surgery which may produce hypotension reflexly. In order to prevent the postoperative complication, these observers recommend a thorough preoperative cardiovascular survey, the early recognition and treatment of hypotension, arrhythmias and congestive heart failure, and careful regulation of the fluid, blood and electrolyte balance after surgery.

ROSENBAUM

Cosby, R. S., Talbot, J. C., Levinson, D. C. and Mayo, M.: The Vector-Electrocardiogram in Acute Coronary Insufficiency and in Acute Myocardial Infarction. Am. Heart J. **49:** 896 (June), 1955.

In 27 patients with acute coronary insufficiency and in 24 patients with acute myocardial infarction, electrocardiograms and mean spatial vectors of QRS and T have been described and compared. Acute coronary insufficiency is a common clinical entity, at least half as common as acute transmural myocardial infarction. The diagnosis of acute coronary insufficiency may be made with reasonable accuracy, and implies an area of subendocardial necrosis which is anterior in location three times as frequently as posterior. The mean spatial vector of QRS, being a composite figure, shows little change in myocardial infarction, and, of course, in coronary insufficiency. The mean spatial T-vector shift is greater in acute myocardial infarction than in acute coronary insufficiency. The maximum shift occurs earlier, on the third day in acute coronary insufficiency, and considerably later in myocardial infarction. In acute myocardial infarction, anterior in location, there is a close correlation between the degree of shift of the mean spatial T vector and the severity of the illness. Thus, in this situation, the degree of shift of the T vector appears to be a measure of the extent of myocardial injury. Complete electrocardiographic recovery occurs more frequently in acute coronary insufficiency. Also, the attainment of a stable electrocardiogram occurs earlier than in acute myocardial infarction. Vector-electrocardiography is of real value in acute coronary insufficiency and in acute myocardial infarction. It is a semiquantitative yardstick for the more detailed appraisal of the degree of myocardial injury and the amount of recovery.

RINZLER

Barr, D. P.: Influence of Sex and Sex Hormones upon the Development of Atherosclerosis and upon the Lipoproteins of Plasma. J. Chronic Dis. **1:** 63 (Jan.), 1955.

Comparative studies have revealed an earlier and greater incidence of coronary and peripheral atherosclerosis in men than in women. Clinically, angina pectoris, coronary occlusion and myocardial infarction rarely occur in women before the age of 40, and arteriosclerotic disease of the vessels of the legs is more common in men. This sex-difference in susceptibility to coronary and peripheral arterial disease cannot be satisfactorily explained by anatomic studies, nor can it be correlated with any demonstrable variation with sex in the concentration of total lipids, cholesterol or phospholipids. Sex-linked differences in the distribution of lipoproteins can, however, be demonstrated by Cohn fractionation or plasma or by the methods of paper electrophoresis and ultracentrifugation. The plasma of young men contains a greater concentration of β-lipoproteins, a smaller amount of α-lipoproteins, a higher β–α ratio and a larger content of S_f 10–20 lipoproteins. Action of heparin in clearing alimentary hyperlipemia is less prompt in young men. The number of mast cells in their tissues is less than in young women. Both the differences in the incidence of clinical complications and in the state of the plasma lipids tend to disappear with aging, particularly after the menopause. That the chemical differences between young men and women have some relationship to the development of atherosclerosis is indicated by the demonstration that states of relative freedom from the disease are accompanied by lipid patterns like those of young women and that diseases and conditions which are accompanied by advanced atherosclerosis, or are known to be atherogenic, have patterns that are exaggerations of those found in young men.

Studies of spontaneous or induced atherosclerosis in the domestic fowl have been helpful, although certain gross species' differences make their application to human disease uncertain. Experimental cholesterol-induced atherosclerosis causes coronary atherosclerosis in the male bird, but not in the laying hen, as well as extensive atheromatous lesions of the aorta in both sexes. Administration of estrogen inhibits prophylactically the development of coronary atheroma, but does not affect lipid deposit in the aorta. Estrogen also has a therapeutic effect in causing regression of coronary atheroma without modifying the degree of aortic atherosclerosis. These anatomic effects of estrogen are accompanied by modification of the chemical changes consequent to cholesterol feeding, and particularly are responsible for an increase in the concentration of phospholipids and a lowering of the cholesterol-phospholipid ratios. They are not reversed in the chick by simultaneous administration of androgen.

In man, the administration of estrogen transforms the highly abnormal lipid pattern of myocardial infarction to one that is indistinguishable from that of healthy young women. Methyl testosterone exerts an opposite action. It exaggerates the lipid abnormality of survivors of myocardial infarction; it produces patterns similar to those of coronary atherosclerosis in individuals whose plasma has previously shown no lipid abnormalities. Contrary to the experience in the chick, the administration of androgens simultaneously with that of estrogens obliterates the chemical effects of the estrogens.

The accumulated clinical and experimental evidence leaves little doubt that sex is a potent factor in the development of atherosclerosis, that its influence is hormonal, and is accompanied by easily recognizable changes in the distribution of lipids in plasma. There is reason to believe that the development of coronary atherosclerosis and its complications is dependent upon factors not equally operative in other arterial systems.

MAXWELL

Chardack, W. M., Bolgan, F. J., Olson, K. C., Gage, A. A. and Farnsworth, W. E.: The Mortality following Ligation of the Anterior Descending Branch of the Left Coronary Artery in Dogs. Ann. Surg. **141:** 443 (April), 1955.

The effect of ligation of the anterior descending branch of the left coronary artery and of other procedures was studied in a series of 22 dogs. All but two survived the initial procedure. It was concluded that mortality studies following experimental coronary ligation were an unsatisfactory tool for the analysis of possible benefits derived from surgical procedures designed to protect the animal from such ligation.

ABRAMSON

Binder, M. J., Ryan, J. A., Jr., Marcus, S., Mugler, F., Jr., Strange, D. and Agress, C. M.: Evaluation of Therapy in Shock following Acute Myocardial Infarction. Am. J. Med. **18:** 622 (April), 1955.

There is need for uniform criteria for the classification of shock following acute myocardial infarction. The authors chose six criteria for determining the presence of, and evaluating therapy in, severe coronary shock: (1) acute myocardial infarction proven by electrocardiogram, autopsy or both, (2) systolic blood pressure 80 mm. Hg or less, pulse rate 110 or more (unless second or third degree A-V heart block is present); (3) clinical signs of peripheral circulatory collapse, marked oliguria or anuria, pallor or cyanosis or both, marked sweating, cold skin, dulled sensorium; (4) no improvement in shock state for one-half hour after relief of pain and administration of oxygen; (5) absence of ventricular or supraventricular tachycardia, severe congestive heart failure, significant pulmonary infarction, recent cerebrovascular accident, diabetic acidosis, hemorrhage, infection and hypotensive drugs; (6) for evaluation of therapy, patient should survive at least one hour after the initiation of treatment. Using these criteria, the authors find Levoarterenol is the vasopressor drug of choice in patients with severe coronary shock. Compared to nonspecific therapy, Levoarterenol is beneficial and may be life-saving in an additional 20 per cent of these patients. Neither intravenous nor intra-arterial transfusions alone reduces the mortality rate in severe coronary shock. The mechanism of coronary shock is obscure and present therapy is empirical. Additional data are needed on the hemodynamic changes and mechanism of this syndrome.

HARRIS

Douglas, D. and Melrose, A. G.: The Relationship of Coronary Atherosclerosis and Chronic Peptic Ulcer. Glasgow M. J. **36:** 147 (May), 1955.

The authors summarize the recent literature (there has been a great amount) on the relationship between peptic ulcer and coronary atherosclerosis, in an attempt to prove a single causal relationship. From a study of the 3,421 post-mortem examinations at the Glasgow Royal Infirmary between 1939–1948, they conclude that there is no direct relationship.

HARVEY

Kennard, M. A. and Haugen, F. P.: The Relation of Subcutaneous Focal Sensitivity to Referred Pain of Cardiac Origin. Anesthesiology **16:** 297 (May), 1955.

Seventy-two patients with cardiac disorders, 35 with thoracic disorders not related to the heart and 45 with nonthoracic disorders were carefully examined in regard to the presence of sensitive areas (trigger sites) over the chest, back and shoulders. Such areas were found in 20 per cent of the individuals without thoracic disease, in 48 per cent of

the patients who had a thoracic disorder not of cardiac origin and in 61 per cent of those with spontaneous cardiac pain. In the cardiac cases, laterality of spontaneous pain was associated with trigger tenderness of the same side. These focal points occurred in specific areas of identical location in all the subjects examined.

On the basis of their findings, the authors suggest that these trigger areas result from focal inflammatory changes arising from reflex vasomotor processes, and that these areas are located in close proximity to the larger and more superficial nerves. A concept is offered for the explanation of the syndrome of referred cardiac pain, postulating that the autonomic stimuli arising from visceral excitation travels to other autonomic afferents from the shoulder and neck which enter the same ganglia, and the same cord segments as do the cardiac afferents. This concept of autonomic-to-automic referral rather than autonomic-to-somatic referral also explains many other types of severe, deep-lying pain which do not follow the usual segmental somatic patterns.

SAGALL

Grossman, L. A. and Grossman, M.: Myocardial Infarction Precipitated by Master Two-Step Test. J. A. M. A. **158:** 179 (May 21), 1955.

Although widely employed, the two-step exercise test must not be considered an innocuous procedure. After the performance of such an exercise test, a patient developed myocardial infarction as demonstrated by the typical T wave changes. At no time did the patient have any substernal pressure or pain, but he did develop unusual dyspnea during the test. The patient was hospitalized and treated with anticoagulants; electrocardiograms during this period showed T wave changes compatible with healing, anterior wall myocardial infarction.

KITCHELL

Wilkinson, C. F.: Effects of Lipotropes and Sitosterol on the Level of Blood Lipids and the Clinical Course of Angina Pectoris. J. Am. Geriatrics Soc. **3:** 381 (June), 1955.

The author reports that γ-sitosterol had no effect in lowering the blood cholesterol level of four patients given 30 to 60 cc. of a sitosterol emulsion every meal, totaling 15 to 30 Gm. of soy sterol per day. Another group of 40 patients with angina pectoris was given a mixture of choline and inositol over varying periods of time and different environmental conditions. The blood cholesterol levels in these patients were measured repeatedly, but showed no lowering on the mixture. Clinically, these patients had continued attacks of angina during treatment periods as well as during control periods. This was measured by the number of nitroglycerine tablets used daily by the patients. No statistical figures are given.

HARVEY

CONGESTIVE HEART FAILURE

Nylin, G.: Blood Volume and Residual Volume of the Heart in Decompensation. Am. Heart J. **49:** 803 (June), 1955.

A method for determining the heart volume in decompensation by labelling the red cells with P^{32} or thorium B is described. Fifty-five patients with cardiac decompensation due to vascular or valvular heart disease were tested. Red cell volume is increased during decompensation, and most of this is due to increase of the residual blood in the heart. Data with reference to residual blood in the heart are obtained from measurement of the heart size by x-rays, together with calculation of a dilution curve.

RINZLER

Gunton, R. W., and Paul, W.: Blood Volume in Congestive Heart Failure. J. Clin. Invest. **34:** 879 (June), 1955.

Blood volume studies were made on 102 patients in heart failure and on 107 control patients. The method of P^{32} tagged red cells was used. Under the conditions of the study, as described in detail in this report, it was found that in general the blood volume in congestive heart failure is greater than normal. This consists of an excess of both red cells and plasma. With compensation, the plasma fraction decreases. The red cell volume decrease is small and occurs more slowly. With the spontaneous reappearance of congestive failure the blood volume usually increases again.

The authors were unable to determine any specific factors associated with the increased volume. Etiologic type of heart disease and the amount of edema would not seem to be factors, except in pulmonary heart disease in which the red cell volume is high. It also appears that congestion may occur with a redistribution of blood to the venous side without an increase in the total blood volume.

WAIFE

Heidorn, G. H. and Schemm, F. R.: The Clinical Use of Corticotropin (ACTH) and Adrenal Corticosteroids in the Therapy of Intractable Edema. Am. J. M. Sc. **229:** 621 (June), 1955.

Of the 33 patients with intractable edema studied there were 10 with nephrotic syndrome, 21 with refractory heart failure and 2 cardiac patients with sodium-dilution syndrome. ACTH and adrenal corticosteroid therapy were utilized in treatment of these patients in a metabolic unit for the determination of sodium and water balances. The program was successful in promoting diuresis in 8 nephrotic, 18 of the 21 heart failure patients and in the 2 sodium depleted patients. According to the authors, the adrenal steroids exert a diuretic effect through suppression of the antidiuretic hormone of the posterior pituitary. It is suggested that patients with longstanding cardiac decompensation have

adrenal insufficiency and excessive antidiuretic hormone levels. The administration of steroids to patients with the sodium-dilution syndrome restored normal sodium and water balances. This form of therapy was found to result in a return of renal tubular sensitivity to mercurial diuretics in patients refractory to their use. The selection of patients to receive this treatment other than refactoriness to usual therapeutic measures remains a problem.

SHUMAN

Frank, M. N., Dreifus, L. S. and Bellet, S.: Hormonal and Electrolyte Influences in Heart Failure. Am. J. M. Sc. **229:** 638 (June), 1955.

The authors investigated the possible hormonal effects in the production of edema in five patients with congestive heart failure. Following establishment of basal conditions, pitressin tannate in oil was administered each morning until maximum effects were observed with water retention and weight gain. At this point, cortisone administration was begun. Both hormones were discontinued when maximum changes were established. In one case the sequence of hormone administration was reversed. Osmotic pressure of the blood and urine was determined by freezing point lowering technique. Sodium and potassium determinations of serum and urine were performed.

Pitressin administration resulted in a reduction of urine volume and weight gain. There was an increase in total urinary solute concentration. All patients developed an increased venous pressure, edema and weight gain not accounted for by decreased urine volume, but was ascribed to thirst and ingestion of water. Upon cessation of Pitressin, there was a diuresis with decreased weight, loss of edema, rise in urine volume and increase in serum total solute and sodium excretion. After cortisone, there was further weight gain and edema formation. Urinary excretion of solute and sodium decreased although urine volume remained constant. The increase in weight was attributed to sodium retention with subsequent water reabsorption. There was no change in total serum solute and sodium concentration with water retention. The two separate mechanisms involved are probably retention of water due to Pitressin, and sodium retention due to cortisone followed by water retention.

SHUMAN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

Prinzmetal, M., Rakita, L., Borduas, J. L., Flamm, E. and Goldman, A.: The Nature of Spontaneous Auricular Fibrillation in Man. J. A. M. A. **157:** 1175 (Apr. 2), 1955.

Direct leads and high speed color motion pictures were recorded of the atria of 15 patients with spontaneous atrial fibrillation before mitral commissurotomy. These studies revealed a chaotic disturbance of atrial activity unlike anything seen during other arrhythmias. Fibrillation consists of heterorhythmic large and small waves occurring simultaneously at rapid and irregular rates. No circus movement was found. In normal rhythm, atrial flutter, tachycardia and extrasystoles, electric and mechanical waves pursue an orderly course from their site of origin to the extremities of the atria. Atrial fibrillation represents a complete breakdown of this orderly activity. Atrial fibrillation may begin with a single extrasystole or be preceded by flutter. In either case there is a breakdown of orderly activity and the rate at which this occurs is termed the fibrillation threshold. Tendency to maintain orderly atrial activity may diminish with age, hyperthyroidism, heart failure or abnormal neurogenic tone. A rapidly discharging ectopic focus is essential to the perpetuation of auricular fibrillation and quinidine by gradually slowing the rate of discharge from such a focus reverses the process of breakdown that characterizes the onset of fibrillation. Orderly flutter waves replace the disorganized fibrillary activity as the rate drops below the fibrillation threshold, and normal sinus rhythm recurs when the focus is inactivated. Clinical and pharmacologic observations appear incompatible with the theory of closing an excitable gap on a circus pathway. More likely drug therapy stops or slows atrial arrhythmias by depressing an ectopic focus. Quinidine and procaine amide seem to depress ectopic foci by raising the threshold of excitability or by lengthening the refractory period. Antiarrhythmic drug action in man may be explained more simply, consistently, and rationally by the ectopic focus theory than by the circus movement theory.

KITCHELL

Van Bogaert, A., Van Geneback, A., Van der Heuts, H., Vandael, J. and Arnoldy, M.: Topographic Value of Unipolar Limb Leads. A Critical Experimental Study. Arch. mal. coeur **48:** 321 (April), 1955.

Following a review of Wilson's concepts concerning the exact meaning of "electrical position" of the heart, and the concept of intracavitary potentials and their applicability to practice, the authors report on a series of experiments bearing on the problem. The first group of experiments consisted of electrically isolating a beating animal heart by means of a rubber glove. This set-up permitted the conclusion that negative potentials in unipolar limb leads do not represent cavity potentials transmitted through the opening at the base of the heart but actually are the reflection of an almost permanent negativity existing in the course of depolarization at the basis of the right ventricle. In a second set of

experiments, the effect of rotations of the heart, along its three axes, upon the behavior of the three unipolar limb leads was studied. This was performed in open-chest animals with the heart surrounded by air, and after the thorax had been filled with a physiologic conducting solution of serum. The records obtained demonstrated clearly that the main factor determining the shape and direction of the QRS complex in the unipolar limb leads is the orientation of the various surfaces of the heart, relative to the point of attachment of extremities, from which the leads were obtained. Additional factors are preferential conduction pathways, or exclusion of certain pathways of electric flow, through inhomogenous conductors varying with the milieu, by which the heart is surrounded. The term electric position is a purely electrocardiographic term and, in order to avoid misconceptions concerning anatomic positions of the heart, should not be used in practical electrocardiography.

PICK

Moreira, J. A.: The Accuracy of the Vectorial Interpretation of Electrocardiographic Tracings. Am. Heart J. **49:** 880 (June), 1955.

This study was undertaken to obtain a method of vectorial interpretation of electrocardiographic tracings which enables one to determine in each case the degree of validity of the vectorial interpretation and accuracy of the vectorcardiographic techniques available. The method chosen by the author consists essentially in the unrestricted admission of the hypothesis necessary for the representation of the cardiac electric field, at each instant, by a vector, and the comparison of the real relations of sets of curves in each subject with those so theoretically predicted. All points for the leads must be located on a continuous convex region of the surface of the body with a spherical electric symmetry.

In such a region, first, the difference of potential between a point P on the thorax and points P_1 equidistant from P is a sinusoidal function of the angle defining and the position of the points P_i and, second, the difference of potential between the point P and conducting ring, including all the points P_i is proportional to the potential at P. The degree with which the first condition is verified may be measured by a correlation coefficient, and the second condition implies that the tracing so obtained must be similar to the unipolar at P, and the quotient of the amplitudes of the two tracings at each instant is a function of the distance of the dipole to the point P. It is supposed that the vectorial interpretation is valid when that correlation coefficient is approximately equal to 1 (or, more practically, when a sinusoidal curve is approximately obtained with the differences of potential measured as referred to in the first condition), and the calculated distances are the same for the dipoles of a cardiac cycle. Methods are given for the calculation of the vectors and the construction of the vectorcardiogram in this case.

RINZLER

ENDOCRINE EFFECTS ON CIRCULATION

Ulrich, F. and Long, C. N. H.: The Effects of Propylthiomocil and Thyrotropic Hormone on the Uptake of Radioactive Thallium by the Rat Thyroid. Yale J. Biol. & Med. **27:** 371 (April), 1955.

It has been shown that after a large dose of radioactive thallium, the greatest amount of the isotope is taken up by the kidney, followed by the colon and the thyroid. The authors undertook to determine whether the thyroid uptake could be influenced by propylthiomocil and thyrotropic hormone. The isotope was injected intraperitoneally into rats, the propylthiomocil was mixed into the feed, and the thyrotropic hormone was injected subcutaneously.

The thyroid uptake of Tl^{204} was increased in the propylthiomocil-treated animals, both on an absolute and on a weight basis. This increase became manifest in eight hours after the injection of Tl^{204}.

Thyrotropic hormone did not release the isotope from the thyroid, but the pretreatment did result in a significant increase in the Tl^{204} content of the gland. The isotope content of blood, plasma, adrenals and pituitary was not affected by either propylthiomocil or thyrotropic hormone.

ENSELBERG

HYPERTENSION

Renwick, R., Robson, J. S. and Stewart, C. P.: Observations upon the Withdrawal of Sodium Chloride from the Diet in Hypertensive and Normotensive Individuals. J. Clin. Invest. **34:** 1037 (July), 1955.

It has been stated that there is a clear difference in response of normotensive and hypertensive subjects to withdrawal of salt. The hypertensives lost less weight and excreted a smaller urine volume in the first 24 hours. In the present report on 6 hypertensive and 6 normotensive subjects on a constant diet, it was found that considerable individual variation in weight and urinary volume exists after abrupt salt withdrawal. However, no consistent difference between normotensive and hypertensive groups was found.

After salt withdrawal and while urinary sodium excretion was diminishing, a temporary increase in urinary potassium excretion was found. There was no associated increase in nitrogen excretion and hence the potassium loss was not due to tissue breakdown. This suggests that increased adrenocortical activity may be an immediate response to the removal of salt from the diet.

WAIFE

Goodyer, A. V. N., Rosenthal, E. and Jaeger, C. A.: The Clinical Evaluation and Management of Hypertension. Yale J. Biol. & Med. **27:** 451 (June), 1955.

The authors have attempted to crystallize a rational approach to the management of the hypertensive patient, based on review of the literature, and their own experience with 56 cases.

Part I. *Evaluation of the Definition, Etiology and Prognosis of Hypertension.* Among the points emphasized, are the advisability of using the muffling of Korotkoff sounds as the best indication of the diastolic level, the frequency of mild postural hypotension in the untreated patient, the frequency of hyperlability of blood pressures, and the significance of diastolic values as compared with systolic values. The intricacy of etiologic mechanisms and the interplay of neurologic, hormonal and renal factors is discussed. An arbitrary scoring method is presented for estimating the severity and prognosis of hypertensive vascular disease, in order to facilitate the choice of a method of treatment.

Part II. *Evaluation of Fundoscopic Findings in Hypertension.* Normal vascular anatomy is briefly reviewed. Vascular changes associated with hypertension result in angiopathy, retinopathy and neuropathy. Angiopathic changes are irregularities (spasms) and narrowing. Retinopathy results in extravasations and infarctions, manifested by flame-shaped hemorrhages, cotton-wool exudates, and edema. Neuropathic changes occur after edema involves the optic nerve, obliterating the disc margins and causing the nerve head to protrude. This finding is associated with hypertensive encephalopathy.

As a consequence of long-standing hypertension, arteriolar sclerosis occurs and this presents a different set of ophthalmoscopic findings: (1) Changes in arteriolar light reflex (widening, "copper wire" arterioles, "silver wire" arterioles); (2) changes in arterio-venous crossings (nicking, compression, angulation of venules); (3) increased tortuosity of both arterioles and venules; and (4) choroidal changes (depositions of pigment and chorioretinal atrophy).

Part III. *Medical Treatment of Hypertension.* The characteristics and methods of administration of the common anti-hypertensive agents are discussed. They include Rauwolfia, Veratrum, Apresoline, and the autonomic ganglionic blocking agents, as well as low-sodium diets. Combination treatments are proposed, based on evaluation of the severity of the disease. Hypertensive crises, such as encephalopathy or pulmonary edema, may be managed by the cautious intravenous use of Veratrum or autonomic blocking agents.

ENSELBERG

Newton, T. H., Smith, G. I., Kolb, F. O. and Smith, D. R.: Successful Use of Regitine (Phentolamine) in the Diagnosis and Surgical Management of a Case of Pheochromocytoma. An Appraisal of Its Clinical Usefulness. New England J. Med. **252:** 974 (June 9), 1955.

The case of a young woman, aged 30 years, with a pheochromocytoma correctly diagnosed and removed with a good result is reported. The classical features of headache, excessive sweating and marked hypertension and manifestations suggesting thyrotoxicosis were present. It is of interest that the benzodioxane test gave a false-negative result. In the discussion of the various diagnostic procedures available in this disorder, the authors point out that those drugs which initiate an attack of hypertension should be used only when the patient is in a normotensive or low hypertensive state. To avoid false-positive reactions, the patients should not be given sedatives for at least 12 hours, or thiocyanates for 4 to 6 days before the test. Histamine is the safest agent and has given the fewest false-positive and false-negative reactions. Mecholyl is not as reliable as histamine and is more dangerous. Agents which lower the blood pressure should be used when the patient is in a definitely hypertensive state; i.e., with levels of 170 systolic, 110 diastolic or higher. Dibenamine is of doubtful value; benzodioxane and Regitine are the agents of choice. When benzodioxane is used, false-positive reactions are not uncommon especially if the patient is uremic, and false-negative reactions are not rare. Regitine is considered the safest of the available adrenolytic agents but false-positive reactions are more common with it than with benzodioxane, especially in patients with uremia, under sedation or with slightly elevated blood pressures. X-ray visualization by means of presacral oxygen insufflation has proven to be an accurate technique and was used to advantage in the case reported. The authors mention that direct estimation of catechols in the blood and urine promises to be a very reliable test for pheochromocytoma. The hazard of the surgical removal of a pheochromocytoma may be reduced by using blocking agents such as Regitine before and during the actual removal of the tumor, and by controlling hypotension after removal of the tumor with infusions of neoepinephrine or epinephrine. In the case reported, there was evidence of relative adrenocortical underactivity as determined by measurement of urinary corticoids prior to the operation with a gradual return to normal over a period of three months after removal of the medullary tumor.

ROSENBAUM

Pastor, B. H., Myerson, R. M., Wohl, G. T. and Rouse, P. V.: Hypertension Associated with Renal Artery Aneurysm and Relieved by Nephrectomy. Ann. Int. Med. **42:** 1122 (May), 1955.

A 36-year old white male complaining of intermittent right flank pain of one and one-half years'

duration which had become worse 10 days prior to admission to the Philadelphia Veterans' Administration Hospital, had been told that he had had hypertension in the past. The elevated blood pressure had been noted on two previous hospitalizations, one for arterial occlusion of the left leg and another for arterial occlusion of the right leg. At the time of his entry to the hospital, the patient's blood pressure was 210/126. There was grade II hypertensive retinopathy, with attenuation and tortuosity of the arterioles and arteriovenous nicking, but no hemorrhages or exudates. The heart was not enlarged. There was a faint systolic murmur at the apex. Although the blood pressure in the legs was unobtainable, normal femoral and diminished dorsalis pedis and posterior tibial pulses were present. Roentgen examination revealed calcification in the arteries of the lower extremities. In a survey film of the abdomen, the right kidney was quite small. However, on intravenous urography, there was excellent concentration of dye in both kidneys in the usual time interval. The renal pelvis on the right, though small, was normal in appearance. Differential renal function studies showed some impairment of function on the right, but total renal function was excellent. An aortogram was attempted but the study was unsatisfactory because of poor visualization of the renal vessels. In an attempt to relieve the peripheral vascular insufficiency, bilateral lumbar sympathectomy was performed; this was followed by considerable improvement in the intermittent claudication. During hospitalization the blood pressure ranged from 160 to 220 systolic and 100 to 150 diastolic, with an average of 180/120 mm. He was readmitted to the hospital because of constant right-sided abdominal pain. He also complained of pain in both groins, particularly on the right, persistent, intermittent claudication and loss of libido. Examination revealed essentially the same findings as on the previous admission. The blood pressure was 190/110 mm. An x-ray of the chest showed slight left ventricular enlargement. The electrocardiogram was normal. A repeat translumbar aortogram revealed a small right kidney measuring 4.5 by 10 cm. The lower pole was poorly visualized, and the upper two-thirds appeared to be supplied with blood by an accessory renal artery arising as a terminal branch of the celiac axis. At the site of origin of the main renal artery there was a rounded density 1.5 by 2.5 cm. This density persisted after the dye had disappeared from the rest of the abdominal circulation. It was interpreted as a saccular aneurysm of the right renal artery, with occlusion distal to the sac. The left renal artery was normal and the left kidney was normally vascularized. An operation revealed a ruptured renal aneurysm with a false aneurysmal sac filled with laminated clot. Right nephrectomy and repair of the aorta at the site of origin of the renal artery aneurysm were accomplished. It was necessary to occlude the aorta just below the diaphragm for 23 minutes. During this period there was no blood flow to the left kidney or to other organs supplied by branches of the aorta below this level, except through their collateral circulation. Following operation the blood pressure fell to 100/70 and gradually stabilized at 110/80 mm. There was marked oliguria for five days, and the blood urea nitrogen rose rapidly to a level of 187 mg. per cent with a creatinine of 13.3 mg. per cent. The blood urea nitrogen gradually fell to a level of 25 mg. per cent, with a creatinine level of 2.0 mg. per cent. The final blood urea nitrogen was 23 mg. per cent. Two weeks after the operation, some difficulty with postural hypotension was experienced by the patient, but it was controlled by elastic bandages and ephedrine. Approximately two and one-half months after the operation, the blood pressure was 120/80 supine and 110/90 mm. in the erect position. Pathologic examination of the kidney confirmed the presence of a large, false aneurysm filled with laminated clot. Microscopic examination of the kidney revealed atrophy and degenerative changes with predominantly tubular involvement. In some areas the changes were said to resemble coagulation necrosis. There was also necrosis in the pelvic region.

WENDKOS

Schroeder, H. A.: Hypertensive Vascular Disease: Therapy with Modern Drugs and its Limits. J. Chronic Dis. **1:** 497 (May), 1955.

The author discusses the rationale, technics, side-effects, limitations and modes of action of modern antihypertensive drugs in the treatment of hypertensive vascular disease. His opinions and recommendations are based on previous data from 400 patients, most of them in complicated or accelerated phases of the disease.

All patients with sustained hypertension, and most patients with fluctuating hypertension, should be treated in an attempt to achieve as normal a cardiovascular state as possible. Sustained control of blood pressure by drugs can be achieved in cooperative individuals in all stages and phases of the disease except the severely azotemic. In almost all severe cases, two approaches have been found necessary; i.e., a drug which influences the neurogenic factor and another which acts on vascular smooth muscle, for a favorable response. The cardinal rule of therapy is to lower blood pressure steadily and slowly until sustained normotension is achieved. Blood pressures must be recorded frequently and combinations and doses of drugs individually tailored. Patience, persistence, and optimism are essential prerequisites for the physician. The only resistant cases are in patients who received intermittent or inadequate therapy. Although we have little understanding of the basic disease, the evidence suggests that prolonged and adequate control of hypertension by drugs reverses the underlying

process, whatever it may be. In any event, many of the secondary vascular effects of hypertension (cardiac, renal, ocular, cerebral) can be prevented.

An appendix to the main article offers specific details of treatment in the various phases of the disease.

MAXWELL

Smithwick, R. H.: Hypertensive Vascular Disease. Results of and Indications for Splanchnicectomy. J. Chronic Dis. **1:** 477 (May), 1955.

The author summarized the 5 to 16 year follow-up of 2,070 patients with hypertension, of whom 1,506 were treated with lumbodorsal splanchnicectomy, and 564 were treated medically. In some patients, both medical and surgical measures were employed, and in other cases no treatment was instituted. The patients were classified in four groups, depending on the severity of the hypertension, retinal changes, renal function and cardiovascular complications; Group 1 were patients with minimal ambulatory hypertension and no secondary changes and Group 4 patients had advanced, severe hypertension with associated complications. A group of 151 patients with accelerated "malignant" hypertension were presented separately.

Actuarial survival curves and five-year mortality rates showed a highly significant difference in outlook for the patients in the various groups in the two series in favor of the surgically treated patients. This difference was most marked in groups 2 and 3 (moderate hypertension with minimal to moderate associated cardiovascular changes). Female patients had a better prognosis than male patients, regardless of the form of treatment. In male patients, the difference in prognosis between surgically and nonsurgically treated patients was somewhat greater than in female patients. Splanchnicectomy exerted its greatest effect on prognosis when operation was performed soon after important changes in the vascular system began to make their appearance (group 2), and even when the abnormalities were moderately advanced and widespread (group 3). Splanchnicectomy rendered patients with the more severe forms of hypertensive vascular disease more susceptible to dietary and drug therapy, as well as to rest. It was noted that since the minimal follow-up was five years, "nonsurgical treatment" in general did not include the newer hypotensive agents developed during the past few years.

Surgically treated patients in the accelerated phase "malignant hypertension" survived longer than nonsurgically treated patients. The status of renal function in this group did not make much difference in the medical series, whereas, in the surgical series the prognosis appeared to be very definitely related to renal function in the sense that if the latter was normal or only slightly decreased at the time of operation, the outlook was much better than when kidney function was moderately or markedly impaired. Although the number of patients in the accelerated phase who were treated medically was small, the results suggested that the treatment employed had little effect upon the mortality rate.

The following therapy is now used by Dr. Smithwick and his associates: (1) Asymptomatic patients with early hypertension are checked yearly for cardiovascular changes and when these occur, medical treatment is instituted; (2) the treatment of patients with more advanced disease depends upon cardiovascular changes and the sex of the individual, group 1 females are treated medically, group 1 males are given a choice, while surgery is recommended as the treatment of choice for all patients falling into groups 2 and 3; (3) group 4 patients are treated surgically if the cardiovascular changes, particularly renal, do not indicate a hopeless prognosis and (4) in the accelerated phase, splanchnicectomy is recommended for patients who still have normal or only slightly reduced kidney function as judged by phenolsulfonphthalein excretion.

MAXWELL

Perera, G. A.: Hypertensive Vascular Disease: Therapeutic Principles and Objectives. J. Chronic Dis. **1:** 472 (May), 1955.

In this introductory article to a symposium on the management of essential hypertension, the author briefly reviews the natural evolution of the disease and considers the objectives to be achieved in treatment.

The disease is divided into three major subdivisions: (1) uncomplicated hypertensive phase, usually lasting about 15 years, either asymptomatic or with intermittent symptoms, such as nervousness, dizziness, headache and palpitation; (2) complications, usually cardiovascular or arteriolosclerotic, and leading to death in approximately five years; (3) accelerated "malignant" phase, with progressive renal damage, retinopathy and encephalopathy, rapidly fatal, which may occur at any time in the course of hypertensive disease.

Because we cannot yet remove the cause of hypertension or prevent the development of pathologic changes, the objectives of treatment are: To educate the patient to live with his disease, to relieve apprehension and fear, to deal with bothersome and sometimes incapacitating symptoms and, if one cannot give added "years of life," then to give "life to years."

There is no convincing proof that any therapeutic measure has lengthened the life of a hypertensive individual in the uncomplicated phase and, indeed, there is uncertainty regarding the relationship of elevated blood pressure, its duration or its height to the complicating pathologic changes. Potentially therapeutic measures must be weighed against their possible undesirable side-effects or risks. Many

therapeutic measures produce dissimilar magnitudes of response and degrees of tolerance when applied to different individuals or in different phases of the disease. Hence, the treatment of each patient must be looked upon as an experiment or as part of a group study, and one is not justified in using the hypotensive response as the sole criterion of improvement.

MAXWELL

Mc Michael, J. and Murphy, E. A.: Methonium Treatment of Severe and Malignant Hypertension. J. Chronic Dis. **1:** 527 (May), 1955.

The principles of methonium or pentolinium treatment of severe and malignant hypertension are reviewed, with emphasis on practical details. Certain hypertensive manifestations, such as headache, retinitis or cardiac strain are reversible by phasic reduction of blood pressure. Other damage of an anatomic nature in blood vessels and other tissue may be irreversible. In malignant hypertension without initial severe uremia, the survival rate seems definitely prolonged by treatment. Amelioration of retinitis and heart failure often permits return to full activity. If gross uremia (blood urea greater than 130 mg. per 100 ml.) is present from the time of recognition of a malignant phase, it is improbable that treatment will be successful in prolonging life. The patient most likely to benefit from methonium treatment is a subject between the ages of 30 and 55 with hypertensive retinitis and predominant cardiac strain, without severe arteriosclerotic complications, such as angina or cerebrovascular accidents, and without renal impairment. Other medical therapeutic measures are considered inferior to parenteral methonium.

MAXWELL

Smirk, F. H. and McQueen, E. G.: Treatment of Hypertension. J. Chronic Dis. **1:** 516 (May), 1955.

In the form of a synthetic panel discussion, the authors answer hypothetical questions on the treatment of hypertension. All patients with an elevated "basal blood pressure" (lowest level to which the blood pressure falls after full sedation) should be treated with drugs. Milder cases are treated with reserpine alone, and more advanced hypertension is treated with combinations of reserpine and a ganglionic-blocking agent, usually pentolinium (Ansolysen). Hypertension secondary to diffuse renal disease (nephritis) or to toxemia of pregnancy should be treated, since there is strong evidence that in all forms of sustained hypertension, if the blood pressure can be reduced for a sufficient part of the 24 hour day, there is amelioration or even disappearance of many reversible clinical manifestations. Most of the vascular changes secondary to hypertension (heart failure, encephalopathy, retinopathy, coronary insufficiency) will regress with adequate therapy; severe renal insufficiency (blood nonprotein nitrogen over 60 mg. per cent), however, usually progresses inexorably to uremia and death despite relief of the hypertension and the associated symptoms.

Individual dosage of, and tolerance to, reserpine and pentolinium are highly variable from one patient to the next. The importance of measuring blood pressure in the standing position is emphasized. The aim of therapy is to lower the systolic blood pressure measured in the standing position to 120 mm. Hg at the trough of the blood pressure fall. The hypotensive effects of the methonium compounds are fully active only when assisted by gravity, and postural hypotension in an integral part of the treatment. The correct dose can often be approximated by increasing the dose in small increments until the patient experiences a feeling of faintness when standing quietly at the time of maximum drug action. The advantage of gravity is also utilized by instructing patients to sleep in a "head up" position.

MAXWELL

Moyer, J. H., Beazley, H. L., McConn, R., Hughes, W., Ford, R. and Dennis, E.: Clinical Results with the Use of Roxinil (an Extract of Rauwolfia Serpentina) in the Treatment of Hypertension. Am. Heart J. **49:** 751 (May), 1955.

Forty patients with essential hypertension of variable severity were treated with Roxinil, an extract of Rauwolfia serpentina containing multiple alkaloids. These results were then compared with those obtained with the alseroxylon fraction as well as the pure alkaloid, reserpine. Roxinil is an effective agent for reducing the blood pressure in patients with hypertension. It reduces the pressure in patients with severe disease as well as in patients with disease of mild to moderate severity. However, the patients in whom the pressure returned to normotensive levels were predominantly from the group with less severe disease. The blood pressure response, side reactions, and general clinical responses with Roxinil were quite similar to those observed with other extracts of Rauwolfia serpentina.

RINZLER

Tuchman, H. and Crumpton, C. W.: A Comparison of Rauwolfia Serpentina Compounds, Crude Root, Alseroxylon Derivative, and Single Alkaloid, in the Treatment of Hypertension. Am. Heart J. **49:** 742 (May), 1955.

Observations on the continued use of reserpine, Raudixin, Rauwiloid and Serpasil in 47 selected patients with arterial hypertension revealed no significant difference in the blood pressure-lowering effect between these agents. The average blood pressure reduction was 35 mm. Hg in the mean arterial blood pressure, a fall which was statistically significant. Successful therapy with Rauwolfia

serpentina depends on an adequate quantity of medication and prolonged administration, the latter being the more important.

RINZLER

Rowe, G. G., Huston J. H. Maxwell, G. M., Weinstein, A. B., Tuchman, H. and Crumpton, C. W.: The Effects of 1-Hydrazinophthalazine upon Coronary Hemodynamics and Myocardial Oxygen Metabolism in Essential Hypertension. J. Clin. Invest. **34:** 696 (May), 1955.

Hemodynamic studies were performed on 11 hypertensive subjects, 6 of whom received Hydralazine and 5 saline solution.

It was found that Hydralazine decreased coronary vascular resistance and increased the coronary blood flow by about 34 per cent. The arteriovenous oxygen difference across the myocardium decreased by 27 per cent, but because of the increased flow the (left ventricular) oxygen consumption remained unchanged.

The reason for the reported precipitation of angina by Hydralazine is not apparent from these results and the authors suggest that angina may develop only in those patients who have a fixed coronary vascular resistance, and, therefore, are unable to compensate for the decreased perfusion pressure. This would result in a reduced coronary flow. It is also possible that Hydralazine directly affects myocardial metabolism so that available oxygen is not utilized and angina is thereby precipitated.

WAIFE

Perry, H. M. Jr. and Schroeder, H. A.: The Use of Pentolinium Tartrate with and without Hydralazine in the Treatment of Severe Hypertension. New England J. Med. **252:** 1057 (June 23), 1955.

This report is concerned with the treatment of 30 severely hypertensive patients with oral pentolinium tartrate. Twelve patients had received no previous antihypertensive therapy, 12 had shown unpleasant side effects from treatment with a combination of hexamethonium chloride and hydralazine and 6 had developed manifestations of collagen disease after treatment with hexamethonium chloride and Hydralazine.

It was found that pentolinium tartrate had advantages over other methonium salts in some patients. Ion for ion, it was ten times as powerful as hexamethonium in lowering the blood pressure and by weight, it was five times as effective as the latter drug. It may produce all of the unpleasant side effects of autonomic blockade although the reactions seemed fewer and milder. It seemed especially useful in those patients who required large doses of hexamethonium but were unable to tolerate it because of unpleasant side-effects. Although relative normotension was produced in some patients with severe hypertension, marked vasomotor instability with severe variations in systolic pressure appeared during pentolinium treatment. In two of the patients with symptoms of collagen disease the dose of hydralazine was reduced to a third and a fifth of the previous amounts, and good blood pressure control with relief of the arthritides occurred with pentolinium tartrate. In two other patients in the collagen disease group, the previous degree of blood pressure control was achieved with treatment with resperine in addition to relatively large amounts of pentolinium. Sodium azide together with pentolinium tartrate failed to control the blood pressure in the remaining two patients who had symptoms of collagen disease when treated with hydralazine and hexamethonium.

When begun before the appearance of frank uremia, the combination of pentolinium tartrate and hydralazine gave satisfactory results in some of the worst cases of hypertension.

ROSENBAUM

Stein, D. H. and Hecht, H. H.: Cardiovascular and Renal Responses to the Combination of Hexamethonium and 1-Hydrazinophthalazine (Apresoline) in Hypertensive Subjects. J. Clin. Invest. **34:** 867 (June), 1955.

Cardiac and renal hemodynamic studies were performed on 18 hypertensive subjects; some receiving Apresoline alone, others Apresoline and hexamethonium. The objective was to see whether a ganglionic blocking agent would alter some of the adverse side-effects occasionally seen after Apresoline.

The observations indicate that a moderately hypotensive dose of hexamethonium does not alter the ability of Apresoline to increase renal plasma flow in some subjects. When Apresoline was administered alone, the cardiac output increased. This increase could be blocked by the prior administration of the ganglionic blocking agent. These observations may offer a rational basis for a therapeutic combination of these drugs; the hypotensive effects are greater, the renal plasma flow may still increase, but there is little increase in cardiac output and cardiac work.

WAIFE

AMERICAN HEART ASSOCIATION, INC.

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Telephone Gramercy 7-9170

SCIENTIFIC SESSIONS ABSTRACTS NOW DUE BY JUNE 15

Abstracts of all papers intended for presentation at the 1956 Scientific Sessions of the Association must be submitted no later than June 15. This represents a month's postponement from the originally announced deadline. The Scientific Sessions are to be held in Cincinnati's Music Hall, October 27–29, in conjunction with the AHA's 32nd Annual Meeting. The complete Association program in the Ohio city is scheduled to run from Saturday, October 27, through Wednesday, October 31.

To be accepted for presentation, papers must be based on original investigations in or related to the cardiovascular field. Abstracts should not exceed 300 words in length and should be submitted in triplicate on special forms provided by the Association.

This year, for the first time papers based on original studies in the areas of interest of the AHA's Council on Community Service and Education will be integrated into the Scientific Sessions' program. For this reason particular attention is called to the Council's invitation to those who wish to report such studies on nutrition, rehabilitation, epidemiology and related fields to submit abstracts before the June 15 deadline date.

Exhibit Applications

June 15 is also the deadline for applying for space to present scientific exhibits at the Sessions. The use of a large public auditorium will enable the Association to greatly expand facilities for both scientific and technical exhibits.

Further information on applications for exhibit space as well as on submission of abstracts may be obtained from the American Heart Association, 44 East 23 Street, New York 10, N. Y. Commercial organizations wishing space for technical exhibits are advised to contact Stephen K. Herlitz, Inc., 280 Madison Avenue, New York, N. Y.

STATEMENT ON SMOKING ISSUED BY AHA

Much greater knowledge is needed before conclusions can be drawn concerning possible causal relationships between tobacco smoking and coronary artery disease according to a statement approved by the Association's Executive Committee.

The statement reflected findings of a committee appointed in 1954 to evaluate available scientific evidence relating to smoking and cardiovascular diseases. Definite knowledge, the Association statement asserted, is limited largely to laboratory and clinical evidence that smoking is "harmful in certain diseases of the peripheral blood vessels of the arms and legs." Cited as a clear demonstration of this was the effects of smoking on those suffering from thrombo-angiitis obliterans (Buerger's disease).

The Association also noted that a "small percentage of persons with known disease of the coronary arteries will develop symptoms and display signs detectable by laboratory tests when they smoke." The statement expresses the feeling that such people may be harmed by smoking.

However, for the large majority of cases, the committee said that it believes that available evidence is not adequate to define the effect of smoking on the heart and coronary vessels and that "much greater knowledge is needed before any conclusions can be drawn concerning relationships between smoking and increased death rates from coronary heart disease." To obtain such knowledge, the statement suggested that it may be necessary to employ "techniques and research methods that have not hitherto been applied to this problem."

In conclusion, the statement urged that a technical committee representing a "wide range of research experience be established to suggest the lines of investigation that may be most productive."

BLAKESLEE AWARDS ENTRIES CLOSE TUESDAY, MAY 1

May 1 is the last day on which entries may be submitted for the 1956 Howard W. Blakeslee Awards competition conducted by the Association. The awards, which carry a minimum honorarium of $500 each, will be made for newspaper and magazine articles, books, radio and television programs and films which were published or produced between March 1, 1955 and March 1, 1956. Recipients will be those who in the opinion of the judges contribute most to public understanding of the cardiovascular system and its diseases.

Entry forms and information on the Blakeslee Awards may be obtained from the Association, 44 East 23 Street, New York 10, N. Y.

AHA TO REVIEW ABSTRACTS FOR INTER-AMERICAN CONGRESS

Research investigators and clinicians in the United States wishing to present papers at the Fifth Inter-American Congress of Cardiology to be held in Havana, November 11–17, should submit abstracts of their papers to the American Heart Association, 44 East 23 Street, New York 10, by July 1. The papers will be reviewed and transmitted to the Congress Committee. This is in accordance with the procedure established by the Inter-American Congress.

Abstracts should be no more than 200 words in length and should be submitted in triplicate. At the Congress itself, each paper will be allotted 10 minutes for presentation and five minutes for discussion. Among the subjects selected for discussion in panels and symposia at Havana are cerebrovascular accidents—diagnosis and modern treatment; treatment of coronary disease; modern aspects of arrythmias; treatment of hypertensive vascular disease; etiology and treatment of atherosclerosis; chronic cor pulmonale; clinical electrocardiography and vectorcardiography; present status of heart surgery.

The program will also include scientific exhibits and technical exhibits on the latest advances in therapeutics and cardiologic equipment. Invitations to present scientific exhibits will be limited to institutional groups. Those interested should obtain additional information from the Congress at the address given below.

Registration fee for the entire Congress, including social events, is $25. Associate registrations for wives and family may be arranged for $10. Money orders should be made out to Dr. Luis Ortega Verdes, Treasurer. All mail with regard to the Congress (excepting abstracts) should be sent to the Fifth Inter-American Congress of Cardiology, Apartado 2108, Havana, Cuba.

ARMED FORCES INSTITUTE PLANS CARDIOLOGY COURSE MAY 14–17

A postgraduate course on diseases of the heart will be conducted for physicians by the Armed Forces Institute of Pathology in Washington, May 14–17. The course is endorsed by the American Heart Association.

Both civilian and military physicians will be eligible to participate in the symposium with enrollment limited to 425 persons. The first day's program will deal with heart embryology, anatomy, histology, the electrical conduction system of the heart and pharmacologic aspects of cardiology. Subsequent programs will be focused on congenital malformations of the heart, rheumatic fever and rheumatic heart disease, coronary atherosclerosis and occlusion and the less common forms of heart disease.

Course director is William C. Manion, M.D., Chief of the Armed Forces Institute of Pathology's cardiovascular section. The Institute is the central laboratory of pathology for the military establishment.

Participants in the symposium will include: Bradley M. Patton, M.D., University of Michigan; Oscar V. Batson, M.D., University of Pennsylvania; Maurice Lev, M.D., Miami, Fla.; Edward Hawthorne, M.D., Howard University; Theodore Koppyani, M.D., Georgetown University; Jesse E. Edwards, M.D., Mayo Clinic; Col. Thomas Mattingly, M.D., Walter Reed Army Hospital; T. F. Hilbish, M.D., National Institutes of Health; Charles Hufnagel, M.D., Georgetown University; T. G. Borilla, M.D., Walter Reed Army Medical Center.

Also Proctor Harvey, M.D., Georgetown University; Major John Maloney, M.D.,

Armed Forces Institute of Pathology; Major Edward Jahnke, Jr., M.D., Walter Reed Army Medical Center; Otto Saphir, M.D., University of Illinois; Charles Friedberg, M.D., Columbia University; Joseph T. Roberts, M.D., Buffalo Veterans Administration Hospital; Colonel Byron Pollock, M.D., Fitzsimons Army Hospital; Walter C. Putschar, M.D., Charleston General Hospital; Sylvester E. Gould, M.D., Wayne County General Hospital; Kenneth R. Mallory, M.D., Boston City Hospital; Frank Johnson, M.D., Armed Forces Institute of Pathology.

Also Lieutenant Colonel Loren F. Parmley, Jr., M.D., Walter Reed Army Medical Center; Richard Follis, M.D., Armed Forces Institute of Pathology; Samuel Rosen, M.D., Armed Forces Institute of Pathology; William Von Glahn, M.D., Louisiana State University; and Richard O'Dell, M.D., Charleston, W. Va.

Civilian physicians who desire to attend may apply directly to the Director, Armed Forces Institute of Pathology, Washington 25, D. C. Doctors in the armed forces should make application through normal military channels.

AHA COMPLETES NEW FILM ON RESEARCH

A film for the general public on cardiovascular research has been completed by the Association. Entitled, "Secrets of the Heart," the motion picture is designed to increase public understanding of medical research and the role of basic scientists in the fight against cardiovascular diseases.

The half-hour picture was produced by MPO Productions and written and directed by George C. Stoney who previously did the prize-winning film on rheumatic fever, "The Valiant Heart," for the Association. "Secrets of the Heart" devotes itself to interviews with research investigators in their laboratories during which the scientists explain and demonstrate their actual work. Irvine H. Page, M.D., President of the Association serves as a scientific guide for the audience.

"Secrets of the Heart" will be distributed through the AHA and state and local Heart Associations, and it is expected that it will be shown on television in many areas.

CANADIAN HEART ASSOCIATION SETS ANNUAL MEETING JUNE 14–15

The eighth annual meeting of the Canadian Heart Association will be held in Quebec City, June 14 and 15. Physicians from the United States will be welcome to participate in the programs.

Additional information on the program and other details affecting attendance at the meeting may be obtained from John D. Keith, M.D., 555 University Avenue, Toronto, Ontario.

CONFERENCE ON MERCURIALS SCHEDULED IN NEW YORK

The New York Academy of Sciences has scheduled a two-day conference on mercury and its compounds for Friday and Saturday, April 6–7, at the Barbizon-Plaza Hotel in New York City. The first day's program will be devoted to the physical and chemical properties of the mercurials, and the second day to clinical applications, with emphasis on the utilization of mercurial diuretics. Among the subjects to be covered will be the clinical effectiveness of mercurial diuretics in congestive heart failure, and out-patient management of the cardiac patient with oral mercurial diuretics.

All physicians and workers in the biologic and physical sciences are welcome to attend sessions which begin at 9 A.M. each day.

MEETINGS CALENDAR

April 15: American Society of Biological Chemists, Atlantic City. Philip Handler, Duke University, Durham, N. C.

April 15–16: American Society for Artificial Internal Organs, Atlantic City. Peter F. Salisbury, M.D., Institute for Medical Research, Cedars of Lebanon Hospital, 4751 Fountain Avenue, Los Angeles 29.

April 15–20: American Society for Pharmacology and Experimental Therapeutics, Atlantic City. C. C. Pfeiffer, Emory University School of Medicine, Emory University, Ga.

April 15–21: American Society for Experimental Pathology, Atlantic City. Cyrus C. Erickson, 874 Union Ave., Memphis 3.

April 24: Scientific Session of the New York Heart Association, New York. J. Murray Steele, M.D., New York Heart Association, 485 Fifth Ave., New York 17.

April 26–28: American Association of Pathologists and Bacteriologists, Cincinnati. Edward A. Gall, Cincinnati General Hospital, Cincinnati 29.

April 27–28: American Gastroenterological Association, Atlantic City. H. Marvin Pollard, University Hospital, Ann Arbor, Mich.

April 29: American Federation for Clinical Research, Atlantic City. William W. Stead, V.A. Hospital, Minneapolis 17.

April 30: American Society for Clinical Investigation, Atlantic City. A. P. DeWeese, 515 East Main Street, Kent, O.

May 1–2: Association of American Physicians, Atlantic City. P. B. Beeson, Yale University School of Medicine, New Haven 11.

May 3–4: American Geriatrics Society, Chicago. Malford W. Thewlis, 25 Mechanic St., Wakefield, R. I.

May 6–11: Society for Pediatric Research, Buck Hill Falls, Pa. Sidney S. Gellis, 330 Brookline Ave., Boston 15.

May 29–June 3: Society of American Bacteriologists, Houston. J. H. Bailey, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

June 7–10: American College of Chest Physicians, Chicago. Murray Kornfeld, 112 E. Chestnut St., Chicago 11.

June 7–10: American Therapeutic Society, Chicago. O. B. Hunter Jr., 915 19th St., N.W., Washington, D. C.

June 8–12: American Medical Women's Association, Chicago. Lillian T. Majally, 1790 Broadway, New York 19.

June 9: North American Chapter, International Society of Angiology, Chicago. Henry Haimovici, M.D., 105 E. 90th St., New York 28.

June 10: Society for Vascular Surgery, Chicago. Henry Swan, 4200 E. 9th Ave., Denver 7.

June 18–20: American Neurological Association, Atlantic City. Charles Rupp, 133 S. 36th St., Philadelphia.

July 23–26: International Congress of Developmental Biology, Providence, R. I. Prof. Paul Weiss, Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21.

July 27–31: Second International Symposium on the Cellular Basis of Differentiation, Providence, R. I. Prof. Paul Weiss, Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21.

ABROAD

April 24–27: Annual Health Congress, Royal Sanitary Institute, Blackpool, England. P. Arthur Wells, Esq., Royal Sanitary Institute, 90 Buckingham Palace Rd., London S.W.1.

April 28–May 5: Third International Conference on Health Education, Rome, Italy. Lucien Viborel, Sec.-Gen. 92 rue Saint-Denis, Paris 1er, France.

May 9: Geneva: 9th World Health Assembly, World Health Organization. WHO, Palais des Nations, Geneva, Switzerland.

May 24–26: First International Congress of Infectious Pathology, Lyon, France. Prof. Sedallian, Pres. of Committee of Organization, 77 rue Pasteur, Lyon, France.

June 20–22: Ciba Foundation Colloquium on Endocrinology: Regulation and Mode of Action of Thyroid Hormone (by invitation), London. Dr. G. E. Wolstenholme, Director of Foundation, 41 Portland Place, London, W.1.

July 22–27: 8th International Congress of Pediatrics, Copenhagen, Denmark. Congress of Pediatrics, Domus Medica, 12A Kristianiagade, Copenhagen.

July 22–28: 8th International Congress of Radiology, Mexico City. Dr. Jose Noriega, Sec. Gen. of Congress, Tepic 126 (2e piso), Mexico City 7.

July 30–Aug. 4: 20th International Physiological Congress, Brussels, Belgium. Prof. J. J. Reuse, Faculté de Médicine et de Pharmacie, 115 Boulevard de Waterloo, Brussels.

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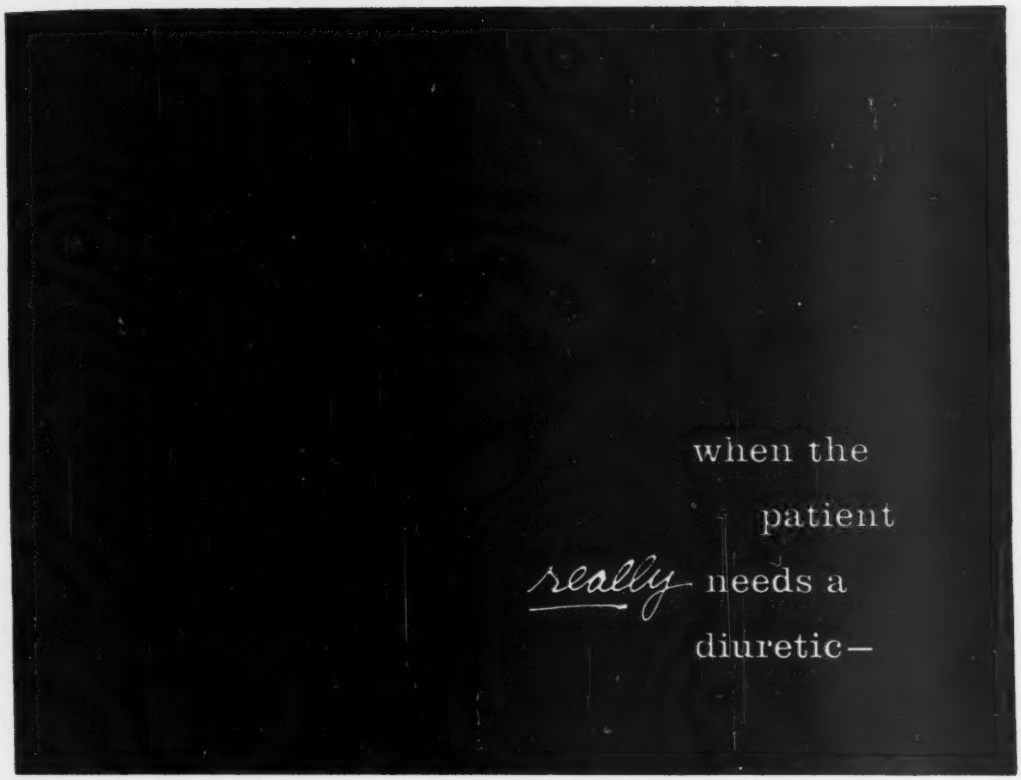

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CONTENTS

EFFECT OF PREGNANCY ON THE COURSE OF HEART DISEASE; RE-EVALUATION OF 106 CARDIAC PATIENTS THREE TO FIVE YEARS AFTER PREGNANCY
Mary M. Miller and James Metcalfe 481

A CONTROLLED STUDY OF THE EFFECT OF INTERMITTENT HEPARIN THERAPY ON THE COURSE OF HUMAN CORONARY ATHEROSCLEROSIS
H. Engelberg, R. Kuhn and M. Steinman 489

THE PERSISTENT OSTIUM PRIMUM ATRIAL SEPTAL DEFECT
S. Gilbert Blount, Jr., Oscar J. Balchum and Goffredo Gensini 499

THE SIGNIFICANCE OF THE INTENSITY AND TIME OF APPEARANCE OF THE KOROTKOFF SOUNDS IN AURICULAR FIBRILLATION
Simon Rodbard and Jack Margolis 510

FLUORESCENT PATTERNS OF INTRACUTANEOUS WHEALS IN NORMAL AND EDEMATOUS EXTREMITIES ..... *Ray W. Gifford, Jr., John H. Windesheim, J. Earle Estes, Jr. and Grace M. Roth* 515

PERIPHERAL VENOCONSTRICTION IN HUMAN CONGESTIVE HEART FAILURE
J. Edwin Wood, Julius Litter and Robert W. Wilkins 524

STUDIES ON THE CONTROL OF HYPERTENSION. VI. SOME EVIDENCE FOR REVERSAL OF THE PROCESS DURING HEXAMETHONIUM AND HYDRALAZINE THERAPY
H. Mitchell Perry, Jr. and Henry A. Schroeder 528

PECTORALIS MINOR TENOTOMY AND ANTERIOR SCALENOTOMY WITH SPECIAL REFERENCE TO THE HYPERABDUCTION SYNDROME AND "EFFORT THROMBOSIS" OF THE SUBCLAVIAN VEIN ..... *Jere W. Lord, Jr. and Peter W. Stone* 537

TOTAL ANOMALOUS PULMONARY RETURN: AN ANALYSIS OF THIRTY CASES
Vincent L. Gott, Richard G. Lester, C. Walton Lillehei and Richard L. Varco 543

OBSERVATIONS ON ANGINA PECTORIS DURING DRUG TREATMENT OF HYPERTENSION
Walter E. Judson, William Hollander and Robert W. Wilkins 553

THE SPATIAL VENTRICULAR GRADIENT: INTERMITTENT WOLFF-PARKINSON-WHITE SYNDROME, INTERMITTENT LEFT BUNDLE BRANCH BLOCK AND VENTRICULAR PREMATURE CONTRACTIONS .... *Mordecai A. Berkun, Russell H. Kesselman, Ephraim Donoso and Arthur Grishman* 562

THE TISSUE CATECHOL AMINE CONCENTRATION OF THE HUMAN HEART DETERMINED BY THE ALUMINUM HYDROXIDE-ARSENOMOLYBDIC ACID METHOD
J. M. B. Bloodworth, Jr. and E. von Haam 573

VECTORCARDIOGRAPHIC NOTATION ..... *Robert A. Helm* 581

HEMOLYTIC SYNDROME FOLLOWING THE INSERTION OF A LUCITE BALL VALVE PROSTHESIS INTO THE CARDIOVASCULAR SYSTEM
Frederick Stohlman, Jr., Stanley J. Sarnoff, Robert B. Case and Arthur T. Ness 586

A TWO-DIMENSIONAL BALLISTOCARDIOGRAPHIC STUDY OF THE RELATION OF BODY SIZE TO BALLISTIC AMPLITUDE IN CHILDREN
Gwendolyn L. Morris and Melville I. Singer 592

CLINICAL PROGRESS. THE MANAGEMENT OF HYPERTENSIVE CARDIOVASCULAR DISEASE ..... *Edward Meilman* 596

AUSCULTATORY DIAGNOSIS OF VALVULAR HEART DISEASE .. *George David Geckeler* 608

SPECIAL COMMITTEE REPORTS.

STANDARDS FOR CENTERS CARING FOR PATIENTS WITH CONGENITAL CARDIAC DEFECTS. REPORT OF THE SUBCOMMITTEE ON EDUCATION AND STANDARDS IN THE FIELD OF CONGENITAL HEART DISEASE 613

JONES CRITERIA (MODIFIED) FOR GUIDANCE IN THE DIAGNOSIS OF RHEUMATIC FEVER. REPORT OF THE COMMITTEE ON STANDARDS AND CRITERIA FOR PROGRAMS OF CARE 617

ABSTRACTS 621

AMERICAN HEART ASSOCIATION 635

CONTRIBUTORS TO THIS ISSUE 639